

# Chronotherapeutic Drug Delivery Systems: An approach to synchronize drug concentrations to circadian rhythms in disease state.

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## Abstract:

Chronotherapeutics is the discipline concerned with the delivery of drugs according to the intrinsic activities of a disease over a certain period of time, on the basis of the observation that there is an interdependent relationship between peak-to-trough rhythmic activity in disease symptoms and risk factors, pharmacologic sensitivity and pharmacokinetics of many drugs. As the effectiveness and toxicity of many drugs vary depending on dosing time associated with 24 hr rhythms of biochemical, physiological, pathological and behavioral processes under the control of circadian clock. If symptoms of a disease display circadian variation, drug release should also vary over time to match the circadian rhythms of the disease. The specific time at which the patients take their medication is very important as it has significant impact on the success of treatment as the optimum clinical outcome cannot be achieved if drug plasma concentrations are constant. For the successful treatment the drug should be delivered at the right site of action at the right time and in the right amount, thus providing minimal side effects with optimum therapeutic effect and increased patient compliance. Thus the time programmed release delivery systems can prove more beneficial than the conventional systems in the era of modern therapies for the patient. Rather than searching the new drugs for the treatment, release modified systems can save much more time of drug discovery process.

## Keywords:

Chronotherapeutics; circadian rhythm; chronopharmacology; chronopharmacokinetics; drug delivery systems;

## Introduction:

Chronotherapeutics refers to a treatment method in which in vivo drug availability is timed to match rhythms of disease, in order to optimise therapeutic outcomes and minimise side effects. It is based on the observation that there is an interdependent relationship between peak-to-trough rhythmic activity in disease symptoms and risk factors, pharmacologic sensitivity, and pharmacokinetics of many drugs.

Drug pharmacokinetics can also be time-dependent; therefore, variations both in a disease state and in drug plasma concentration need to be taken into consideration in developing drug delivery systems intended for the treatment of disease with adequate dose at appropriate time. Various technologies such as time-controlled, pulsed, triggered and programmed drug delivery devices have been developed and extensively studied in recent years for chronopharmaceutical drug delivery. These, as well as pertinent issues, are addressed in this review <sup>[1]</sup>.

Many functions of the human body vary considerably in a day. These variations cause changes both in disease state and in plasma drug concentrations. Human circadian rhythm is based on sleep-activity cycle, is influenced by our genetic makeup and hence, affects the body's functions day and night (24-hour period).

Several pulsed-release formulations have been developed recently. Tablet-based or capsule-based pulsatile/delayed-release formulation is the basis of the new drug delivery technology that addresses emerging chronotherapeutic requirements. For example, in cardiovascular diseases the focus is to optimally deliver the antihypertensive and/or antianginal drug in higher amounts in early morning hours (i.e. at time of greatest need) and lower amounts at night (i.e. at the middle of sleep cycle when the need of drug is less). The patients have to take such tablet or capsule at bedtime daily. A number of such drug delivery systems have been developed for timed release of antihypertensive/antianginal agents such as verapamil, diltiazem and propranolol <sup>[2]</sup>.

## Biological rhythms

A biological rhythm is a self-sustaining oscillation of endogenous origin. The spectrum of biological rhythms is broad as displayed in Table 1. Short-period rhythms of a second or so are quite common; the high frequency oscillations in the electrical impulses of the central and autonomic nervous systems and the high frequency pulsatile secretions of the neuro endocrine system are but a few examples. Intermediate-period rhythms show oscillations as short as a few hours to as long as 6 days. Included in this category are the ultradian light intensities are thought to be the major environmental cue involved in circadian entrainment. Light- signals are perceived by photoreceptor cells in the retina and transmitted to neurons of the SCN via the retinohypothalamic tract. A great deal of research shows that the inherited period of the human pacemaker clock is not precisely 24 h. In fact, in most people, it is somewhat longer, closer to 25 h. Environmental times, termed synchronizers or zeitgebers, the strongest one being the daily light–dark cycle occurring in conjunction with the wake–sleep routine, set the inherited pacemaker circadian timekeeping systems to 24h each day <sup>[3]</sup>.

## CIRCADIAN RHYTHMS IN OCCURRENCE AND SEVERITY OF DISEASE

### 1) Bronchial Asthma

Airway resistance, bronchoconstriction and exacerbation of symptoms increase progressively at night in asthmatic patients. Risk of asthma attack is 100-fold greater during night time sleep than during daytime activity. Chronotherapy for asthma is aimed at getting maximal effect from bronchodilator medications during early morning hours. Daily or alternate day, morning dose of glucocorticoid medications such as methyl prednisolone (Medrol) significantly moderates side effects and enhance therapeutic benefits. Oral prednisolone administered at 3 pm rather than at 8 am has been shown to be highly effective in the treatment of nocturnal asthma. Evening once daily dosing of controlled release theophylline tablets (Uniphyll 400 mg tablets) showed chronotherapeutical potential in the treatment of nocturnal and earlymorning asthma. Many circadian dependent factors appear to contribute to the worsening of nocturnal asthmatic symptoms<sup>[4]</sup>. For example, cortisol (an antiinflammatory substance) levels were highest at the time of awakening and lowest in the middle of the night, and histamine (a mediator of bronchoconstriction) concentrations peaked at a level that coincided with the greatest degree of bronchoconstriction at 4:00 am.

### 2) Pain

Pain threshold does not follow the same pattern in all tissues. The sensitivity threshold of the gingival to a cold stimulus was maximal at 18:00 h and reached a peak at 03:00 h (35% difference). Tooth sensitivity was lowest between 15:00 and 18:00 h, with a peak in pain intensity at 08:00 h (160% increase). Circadian rhythms in acute pain have been also recorded, such as in dental surgery, with a morning peak during the first postoperative day. The peak of morphine use occurred at 09:00 h and was the least at 15:00 h in patients undergoing elective surgery. The peak demand for morphine or hydromorphone occurred in the early morning and was lowest during the night in postoperative gynecologic patients <sup>[5]</sup>.

### 3) Arthritis

Patients with osteoarthritis tend to have less pain in the morning and more at night; while those with rheumatoid arthritis, have pain that usually peaks in the morning and decreases throughout the day. Chronotherapy for all forms of arthritis using NSAID's such as ibuprofen should be timed to ensure that the highest blood levels of the drug coincide with peak pain. For osteoarthritis sufferers, the optimal time for a nonsteroidal anti-inflammatory drug such as Ibuprofen would be around noon or midafternoon. The same drug would be more effective for people with rheumatoid arthritis when taken after the evening meal. There is a circadian rhythm in the plasma concentration of C - reactive protein and interleukin-6 of patients with rheumatoid arthritis. Symptoms of rheumatoid arthritis are most intense when awaking from night time sleep, while those of osteoarthritis are worse in the evening or at night <sup>[6]</sup>. Chronopharmacological studies of once daily sustained release indomethacin preparation for the treatment of osteoarthritis have indicated that time of dosing influences tolerances and effectiveness.

## 4) Cardiovascular diseases

Several functions (e.g. BP, heart rate, stroke volume, cardiac output, blood flow) of the cardiovascular system are subject to circadian rhythms. For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Platelet aggregability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hyper coagulability of the blood. It was postulated that modification of these circadian triggers by pharmacologic agents may lead to the prevention of adverse cardiac events. Cardiac events also occur with a circadian pattern. Numerous studies have shown an increase in the incidence of early-morning myocardial infarction, sudden cardiac death, stroke, and episodes of ischemia<sup>6</sup>. BP is at its lowest during the sleep cycle and rises steeply during the early morning awakening period. Most patients with essential hypertension have a similar circadian rhythm of BP as do normotensive persons, although hypertensive patients have an upward shift in the profile<sup>7</sup>. They have quite a marked rise in blood pressure upon awakening - called 'the morning surge' - that increase can be 3 mm Hg/hour (systolic) and 2mm Hg/hour (diastolic) for the first four to six hours after waking up. This is due to high catecholamine concentration in the early morning.

## Chronopharmacokinetics

Chronokinetics refers to dosing-time, i.e., rhythm-dependent, differences in the absorption, distribution, metabolism, and elimination of medication. Circadian rhythms in gastrointestinal pH can affect drug dissolution, and circadian rhythms in gastric emptying, motility, and blood flow can affect the rate, and in certain cases the amount, of drug absorption. Moreover, circadian rhythms in hepatic blood flow and enzyme activity can significantly affect drug biotransformation and metabolism, and rhythms in hepatic bile function and flow as well as renal blood flow, glomerular filtration, and tubular function can affect drug elimination. The pharmacokinetics, for example, the parameters of the time to peak concentration, peak height, elimination rate, volume of distribution and area under the time-concentration curve, of a number of medications have been found to be influenced by circadian rhythms.

Ideal characteristics for chronotherapeutic drug delivery systems should

- Associate with real time and specific triggering biomarkers for a given disease state.
- Be biocompatible and biodegradable.
- Non-toxic with the usage of delivery systems.
- Self-regulated and adaptive capability to circadian rhythms
- Advantages
- Reduced frequency in dosage schedule
- Improved patient acceptability and compliance
- Minimization of side effects
- Biological tolerance
- Protection of stomach mucosa from gastric irritation drugs
- Drugs with high first pass effects can be delivered efficiently without loss of drug
- Drug targeting to specific sites such as colon is possible

Limitations of pulsatile drug delivery system

- Multiple manufacturing steps in multiparticulate pulsatile drug delivery system.
- Low drug load.
- Incomplete release.
- In-vivo variability in single unit pulsatile drug delivery system.

**Classification of pulsatile drug delivery systems**

Pulsatile drug delivery system is classified into four classes:

Time controlled pulsatile release

Single unit system

- i. Capsular system
- ii. Port system

- iii. iii. Delivery by solubility modulation
- iv. iv. Delivery by reservoir systems

#### Multi-particulate system

- i. Pulsatile system based on rupturable coating (Time controlled expulsion system)
- ii. Pulsatile delivery by change in membrane Permeability
- iii. Sigmoidal release system
- iv. Low density floating multiparticulate pulsatile systems

#### Stimuli induced

##### Internal stimuli induced pulsatile system

- i. Temperature induced system
- ii. ii. Chemical stimuli induced system
- iii. iii. pH sensitive drug delivery system

##### External stimuli induced system

- i. Electrically stimulated Pulsatile system
- ii. Magnetically stimulated Pulsatile system
- iii. Ultrasonically stimulated Pulsatile system

#### Pulsicap system:

It consists of a water insoluble capsule body filled with the drug and a cross-linked hydrogel plug which swells upon contact with dissolution medium or gastro intestinal fluids pushing it out of the capsules.

#### Port systems:

It consists of a gelatine capsule in a cellulose acetate semi permeable membrane and inside insoluble plug and osmotically active ingredient along with the drug. When it imbibes the gastric fluids resulting in increased inner pressure that ejects the plug after a lag time.

#### Delivery by solubility modulation:

Systems composites of modulated agents sodium chloride and drug, lesser amounts of NaCl is required to maintain saturated fluid entering the osmotic device which facilitates pulse release.

Delivery by reservoir system with erodible or soluble barrier coatings: Barrier layer was coated over to the reservoir device of pulsatile drug delivery where the barrier erodes or dissolves after a specific lag period enabling the drug to get released rapidly from the reservoir core.

Multiparticulate system: Drug release from these systems depends on parameters such as type of coating, pH dependent coating, insoluble coating under all physiological conditions influences the solubility changes at some point in G.I. tract and facilitates slow erosion.

Reservoir with rupturable polymeric coating or time controlled explosion system: Super-disintegrants incorporated in as swelling agents facilitating the time burst release of particulates upon ingress of water. Initially the drug coated on non-peril seeds followed by a swellable layer and an insoluble top layer coating. In vitro in vivo correlation studies reported that time controlled explosion systems with a lag time of 3 hrs appearance of drug in blood and maximum release noted after 5 hrs.

Sigmoidal release systems: It consists pellets comprising of different acids such as succinic acid, acetic acid, glutamic acid, malic acid, citric acid, coated with ammonia methacrylate copolymer usp/ nf type b. water influx turns the drug core to acid solution in turn increases the permeation of the hydrated polymer film.

Low density floating multiparticulate pulsatile systems: Especially for the drugs having absorption window in the stomach low density floating micro particle pulsatile dosage forms retain the drug in stomach for a longer period and not influencing by the pH fluctuations and gastric emptying.

Thermoresponsive pulsatile release: Hydrogels at their transient temperatures undergo substantial reversible volume changes in response to change in temperature. Among the various polymers available N-isopropylacrylamide is probably the most extensively used.

Chemical stimuli induced pulsatile release: Stimuli sensitive delivery systems release the drug in presence of biological factors like enzymes, pH or any other chemical stimuli example; Development of a gel composed of poly-N-isopropylacrylamide with phenylboronic acid moieties that showed a remarkable change in the swelling induced by glucose.

pH sensitive drug delivery systems: pH dependent polymers enabled the drug to release in the desired pH range such as eudragit, phthalates, carboxy methyl cellulose, methacrylic acid especially polymers like eudragit L and S favoured the colon targeting .

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