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Editorial

Chronotherapeutics and Drug Delivery: A Review

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ABSTRACT

This writing aims at knowledge of time matched delivery of drugs for obtaining optimum therapeutic benefits of drug. The human body follows the day and night adaptations known as biological clock. The biological clock follows the main rhythm known as circadian rhythm. Chronotherapeutics is treatment method in which *in vivo* drug availability is timed to meet rhythms of disease, in order to optimize therapeutic outcomes and minimize side effects. This approach is highly scientific to design the drug delivery systems.

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INTRODUCTION

Chronotherapy dates back to 1970's, Jean-Jacques d'Ortous de Mairan was the first researcher to take note of the 24-hour patterns occurring in the movement of a plant. Since then, research was done to study the cycle in humans (1). The human body follows the solar/ lunar adaptations known as biological clock. The biological clock follows the main rhythm known as circadian rhythm (2). Rhythmic changes in metabolic events with time is termed as "Chrono" Chronotherapeutics = treatment method in which *in vivo* drug availability is timed to meet rhythms of disease, in order to optimize therapeutic outcomes and minimize side effects (3). Chronotherapeutic based drug delivery (ChDDS) aims at *in vivo* drug availability based on the biological rhythms there by mitigating the unwanted effects and precisely targeting the treatment.

CHRONOBIOLOGY

It is the study of biological rhythms and their mechanism. Types of mechanical rhythms in our body are (1, 4)

ROLE OF CIRCADIAN RHYTHM IN DISEASES

The following diseases follow biological rhythm and hence chemotherapy can be significantly applied (2)

IDEAL CHARACTERISTICS of ChDDS

1. Non-toxic within approved limits of use.
2. Should have a real-time and specific triggering biomarker for a given disease state.
3. Should have a feed-back control system (e.g., self-regulated and adaptative capability to circadian rhythm and individual patient to differentiate between awake–sleep status).
4. Biocompatible and biodegradable, especially for parenteral administration.
5. Easy to manufacture at economic cost.
6. Easy to administer in to patients in order to enhance compliance to dosage regimen (5).

REGULATORY REQUIREMENTS

These Chronotherapeutics fall under the 505 (b)(2) filing, no preclinical studies are performed when these formulations are reformulated against existing products. Label claims are made as per reference listed drug (RLD), and preclinical safety is referred to RLD or literature reports. The minimum requirements are:

1. Effect of food on bioavailability of the drug.
2. Dose proportionality study if dose titration is required by the physician.
3. Placebo-controlled phase III studies to establish safety and efficacy and steady-state PK.
4. Single and multidose phase I studies to evaluate safety and bioavailability parameters against reference drug (6).

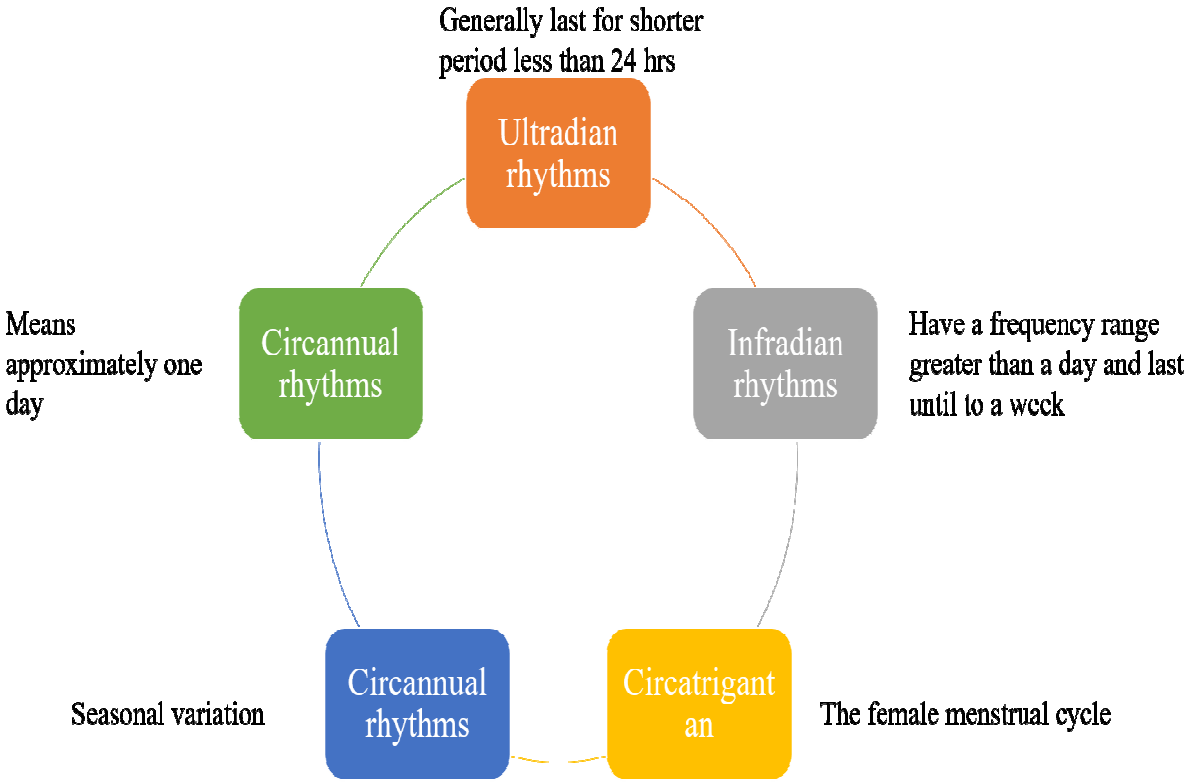

Figure 1: Types of rhythms in body

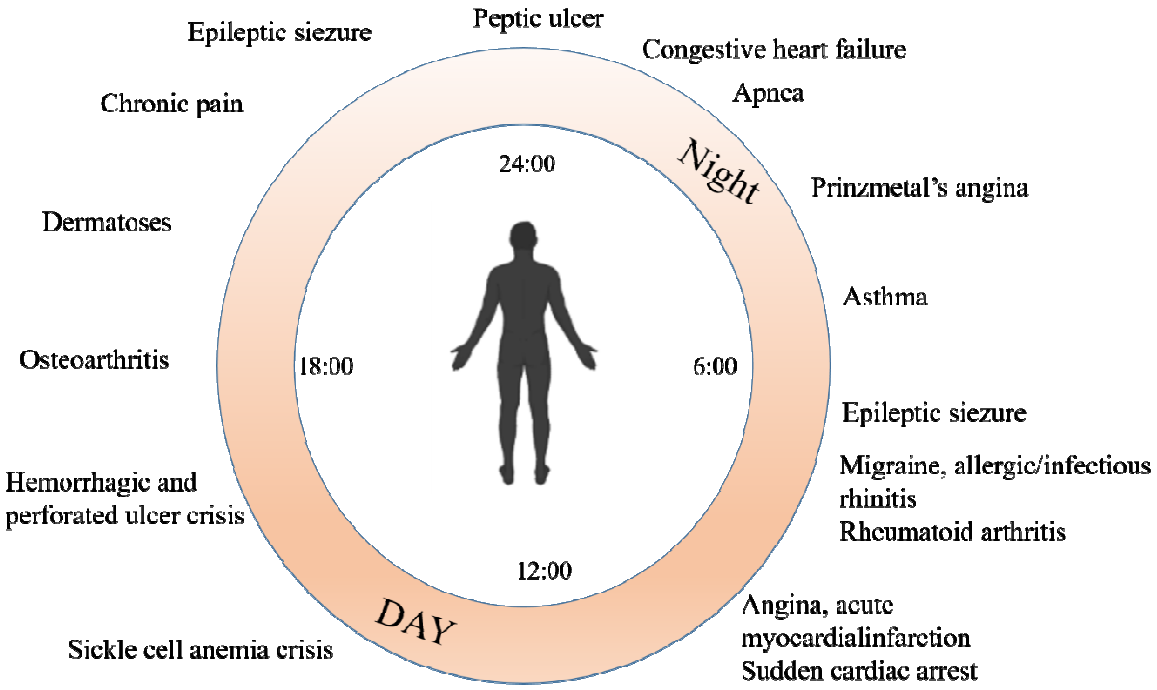

Figure 2: Various diseases that are influenced by the 24h circadian rhythm

Table 1: FDA applications

Application type	Major data requirement	New Indication	New Chemical Entity	New Dosage Form	New formulation	New strength	Can be patented	Market exclusivity
505 (b)(1)	Full safety and efficacy studies and preclinical studies	YES	YES	YES	YES	YES	YES	14 Y
505 (b)(2)	FDA findings for safety and efficacy of a drug data from published literature with no right-of-reference to raw data	May be	May be	May be	May be	May be	YES	3-7 Y
505(j)	Bioequivalence studies	NO	NO	NO	NO	NO	NO	If first generic or against other generic product

CLASSIFICATION

1.1. Based on delivery system

1.1.1. Time controlled

1.1.1.1. Single unit system

A) Capsular system

B) Port system

C) Delivery by solubility modulation

D) Delivery by reservoir systems

1.1.1.2. Multi-particulate system

A) Pulsatile system based on rupturable coating (Time controlled expulsion system)

B) Pulsatile delivery by change in membrane Permeability

C) Sigmoidal release system

D) Low density floating multiparticulate pulsatile systems

1.1.2. Stimuli induced

1.1.2.1. Internal stimuli induced pulsatile system

A) Temperature induced system

B) Chemical stimuli induced system

C) pH sensitive drug delivery system

1.1.2.2. External stimuli induced system

A) Electrically stimulated Pulsatile system

B) Magnetically stimulated Pulsatile system

C) Ultrasonically stimulated Pulsatile system (4)

1.2. Based on route of delivery

1.2.1. Oral

1.2.1.1. CODAS® (Chrono therapeutic Oral Drug Absorption System)

1.2.1.2. Contin® technology

1.2.1.3. Ceform® technology

1.2.1.4. Diffucaps® technology

1.2.1.5. Diffutab®

1.2.1.6. SODAS® (Spheroidal Oral Drug Absorption System)

1.2.2. Transdermal

1.2.2.1. Crystal reservoir system

1.2.2.2. Chemical oscillator

1.2.2.3. Chronodose™ system

1.2.3. Implants

1.2.3.1. Chrono modulated infusion pumps

1.2.3.2. Microfabrication

1.2.3.3. Magnetic nanocomposite hydrogel (5)

2. Description of various systems:

2.1. 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 (7).

2.2. Port systems: It consists of a gelatin 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.

2.3. 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 (8).

2.4. 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 (9).

2.5. 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 (10)

2.6. 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 (11, 12). *In vitro-in vivo* correlation studies reported that time controlled explosion systems with a lag time of 3 h appearance of drug in blood and maximum release noted after 5h (13).

2.7. 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 (14).

2.8. Low density floating multiparticulte 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.

2.9. Thermo responsive 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(15).

2.10. 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-isopolyacrylamide with phenylboronic acid moieties that showed a remarkable change in the swelling induced by glucose (16).

2.11. 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 favored the colon targeting (17, 18).

2.12. Electro responsive pulsatile release: Drug release is facilitated by the action of applied electric field on rate controlling membrane containing polyelectrolytes (18, 19).

2.13. Magnetically induced pulsatile system: With the incorporation of

magnetic materials such as magnetite, iron, nickel, cobalt in to capsule or tablets by the external influence of magnetic field. We can position drug at a specific place or slow down its access to unwanted sites thus changing the time or extent of drug absorption in to stomach or intestine (20).

2.14. Ultrasonically stimulated: Interaction of ultrasound with biological tissues, improving the drug permeation through biological barriers, such as skin. Mechanism mainly involved here is the absorption of acoustic energy by the fluids or tissues and oscillating bubbles cause non-thermal effect along with the non cavitational effects such as radiation pressure, radiation torque and acoustic streaming (21).

Table 2: Marketed products of chronotherapeutic drug delivery systems

Technology	Rationale	Products	Company
CONTIN®	Drug blended with hydrophilic cellulose, then hydrated with polar solvent and fixed with a higher aliphatic alcohol to produce a semi-permeable matrix with uniform porosity.	Uniphyl® once daily theophylline MS Contin® and Oxycontin® for use in pain management.	Purdue Frederick, Norfolk, CT, USA
CODAS®	Chrono-therapeutical oral drug absorption system consisting of drug loaded beads that are coated with release-controlling polymer. Polymer consists of water-soluble and water-insoluble polymers to induce a lag time.	Verelan® PA containing verapamil for use in hypertension	Elan Drug Technologies, San Francisco, CA, USA
CEFORM®	Biodegradable polymers/bio-actives are subjected to varying temperature, thermal gradients and flow processes to produce microspheres of uniform size and shape (150-180µm)	Cardizem® LM containing diltiazem for use in hypertension.	Fuisz Technologies, Chantilly, VA, USA
DIFFUCAPS®	A multiparticulate system consisting of an inactive core,	Innopran® XL containing	Eurand Pharmaceuticals

	coated with an active pharmaceutical ingredient mixed with a water-soluble composition. This may be in the form of beads, pellets or granules.	Propranolol for use in hypertension.	LTD, Dayton, Ohio, USA
GEOMATRIX®	The controlled release is achieved by constructing a multilayered tablet made of two basic key components; 1) hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) and 2) surface controlling barrier layers. Active loaded core surface that is available for drug release when exposed to the fluid is controlled by barrier layers.	Sular® (nisoldipine CR) and Coruno® (molsidomine)	SkyePharma, Muttenz, Switzerland
TIMERx®	A novel polysaccharide system that adopts the use of xanthan gum and locust bean gum in the presence of secondary and tertiary components, to form water-soluble granules.	'Tablet within a tablet' to obtain different chronotherapeutic profiles. Geminex® is an improvement which provides the potential for dual therapy.	Penwest Pharmaceuticals, Danbury, CT, USA
OROS®	As osmotic pump system comprising a central drug reservoir surrounded by a semi-permeable membrane, which is surrounded by osmotically active agents in tablets with a strategically laser-drilled orifice.	Covera® HS containing verapamil for use in hypertension	Alza Corporation, Mountainview, CA, USA
PULSINCAP®	Consists of a drug reservoir housed within a water-soluble capsule body. The open end is plugged with swellable polymers that are pushed out when in contact with fluid, releasing drug	A versatile system that can create lag times as well as allowing tablets/ minitablets, solutions or beads	R.P. Scherer International Corporation, Troy, MI, USA

	from the reservoir.	to be housed within the capsule body.	
PULSYSTM	A novel pulsatile release technology that consists of one immediate-release and two delayed-release components with the use of soluble and insoluble coatings.	Moxatag^{TM} containing amoxicillin for use in antibiotic therapy.	Middlebrook Pharmaceuticals, Westlake, Texas, USA

CONCLUSION: Chronotherapeutics drug delivery is an emerging field of research under pharmaceutical science This approach is highly scientific to design a drug delivery system. It has vast scope for researchers to do novel work for the benefits of society and patients in particular.

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