



CHRONOMODULATED DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

In this review, the concepts of biological rhythms, chronobiology, chronopharmacology, and chronotherapy for various diseases have been discussed. Chronopharmaceutical Drug Delivery Systems (ChrDDS) is a novel system which provides a pattern of real-time drug input at different release rates and it may be achieved by stimuli-sensitive and pulsatile drug delivery systems. 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. A number of chronotherapeutic medications, aiming at synchronizing medications and the intrinsic biorhythms of disease have been developed by novel drug delivery technology.

Key words: Chronobiology, Chronomodulated drug delivery system, Circadian rhythm, Pulsatile drug delivery system.

INTRODUCTION

Biological rhythms are an adaptive phenomena relating to predictable changes in environmental factors that regulate many body functions like metabolism, sleep pattern, hormone production and physiology. Variations in body functions cause changes both in disease state and in plasma drug concentrations. They are predictable resonating dynamic systems, which require different amounts of drug at predictably different times within the circadian cycle in order to maximize desired and minimize undesired drug effect. Here, the concept of Chronopharmaceutics arises. Chronopharmaceutics is a branch of pharmaceutics (science and technology of drug dosage forms) devoted to the design and evaluation of drug delivery systems that release a bioactive agent at a rhythm that ideally matches in real time the biological requirement for a given disease therapy or prevention 'Chronopharmaceutic Drug Delivery System' uses the basic concepts of human chronobiology and the rhythm dependence of certain disease states and the pharmacodynamics of medications. The drug therapy can be optimized by tailoring the dosing schedule based on chronobiological pattern. The safety and efficacy of the drug is achieved by coordinating the peak plasma concentration of the drug with circadian rhythm of the body. Chronotherapy is especially relevant, when the risk and/or intensity of the symptoms of disease vary predictably over time as exemplified by arthritis, asthma,

myocardial infarction, congestive heart failure, stroke, peptic ulcer disease, cancer and many more. Diseases, such as hypertension, asthma, peptic ulcer, arthritis, etc, follow the body's circadian rhythm. Many systems in the human body such as cardiovascular, pulmonary, hepatic and renal systems show variation in their function throughout a typical day. They are naturally synchronized by the internal body clocks and are controlled by the sleep wake cycle. Each bodily system exhibits a peak time of functionality that is in accordance with these rhythmical cycles. Similarly, disease states affect the function of some of these systems in the body and therefore, they too exhibit a peak time of activity within a circadian rhythm. This can be understood by taking an example of Pain. Many new drug formulations, new products, and new drug delivery systems have been developed, but pain treatment is still inadequate. We are convinced that not enough attention has been given to time- of -day patterns of pain intensity and medication requirements. The pain intensity is rarely constant over a 24- hour period. Indeed, many clinical studies report during a day time or active at night episodes of pain exacerbation. Therefore, when asking a patient about the characteristics of his/her pain, it is as important to be precise not only where or how it hurts but also when the pain is least and worse. In fact, several studies have been conducted over the years on the time dependent variation in the perception of pain, its neurochemistry, and

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on drug treatment. The daily pain profile must be used to determine the best time to administer an analgesic drug to a patient. The concept of Chronopharmaceutics, current technologies and approaches towards ChrDDS, potential disease-targets, classification of ChrDDS, and hurdles in development and research are summarized in present review article [1,2,3,4].

IDEAL CHARACTERISTICS OF CHRDDS

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 parental administration.
5. Easy to manufacture at economic cost,
6. Easy to administer in to patients in order to enhance compliance to dosage regimen.

Advantages

- Predictable, reproducible, and short gastric residence time.
- Less inter- and intra-subject variability.
- Improves bioavailability.
- Reduced adverse effects and improved tolerability.
- Limited risk of local irritation.
- No risk of dose dumping.
- Flexibility in design.
- Ease of combining pellets with different compositions or release patterns
- Improves stability.
- Improves patient comfort and compliance.
- Achieves a unique release pattern.
- Extends patent protection, globalizes the product, and overcomes competition.

DISADVANTAGES

- LOW drug loading.
- Proportionally higher need for excipients.
- Lack of manufacturing reproducibility and efficacy.
- Large number of process variables.
- Multiple formulation steps.
- Higher cost of production.
- Need of advanced technology.
- Trained / skilled personnel needed for manufacturing.

OROS® OR CHRONOSET TECHNOLOGY

Chronset™ is a proprietary OROS® delivery system that reproducibly delivers a bolus drug dose, in a time- or site-specific manner, to the gastrointestinal tract. It is nothing but an osmosis-based system. The active pharmaceutical is kept in a reservoir surrounded by a semi permeable 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

(Fuisz Technology Ltd., USA)

It produces uniformly sized and shaped microspheres of pharmaceutical compounds. 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.

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 (semi permeable matrixes), which may be varied. 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.

DIFFUCAPS® technology

In the DIFFUCAPS® technology, 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 Propranolol 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., hydroxypropyl methylcellulose, 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.

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 minitables and pellets have been employed as the inner drug formulation.

EGALET® technology (Egalet Ltd, Denmark)

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. 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 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. The rate of release is independent of pH, posture, and food.

GeoClock® technology

The concept is designed on the basis of Geomatrix technology. 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 (16)

The Programmable Oral Release Technologies (PORT) system is a uniquely coated, encapsulated system that can provide multiple programmed release of the drug. 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. 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. This technology is the basis of the TheriForm technology.

TIMERx® technology

It is a hydrogel-based, controlled release device. This technology can provide from zero order to chronotherapeutic release. 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.

Biological rhythms Ultradian Rhythms

Oscillations of shorter duration are termed Ultradian Rhythms (more than one cycle per 24 h). E.g.90 minutes sleep cycle.

Infradian Rhythms

Oscillations that are longer than 24 hours are termed as Infradian Rhythms (less than one cycle per 24hours). E.g. Monthly Menstruation.

Circadian rhythms

Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 Hours. Interestingly, the term circadian is derived from the Latin circa which means “about” and dies which can be defined as “a day”. Normally, circadian rhythms are synchronized according to internal biologic clocks related to the sleep-wake cycle. Our circadian rhythm is based on sleep-activity cycle and is influenced by our genetic makeup and thereby affects our bodies’ function throughout day and night (24-hour period). Circadian rhythm regulates many body functions in humans like metabolism, physiology, behavior, sleep pattern, hormone production. There are number of conditions which show circadian pattern and advantage could be taken by timing

and adjusting the administration of drugs according to the circadian rhythm of the disease.

Control release systems for 12 or 24 hr drug release are not suitable for diseases, which follow circadian variation. In that condition there is requirement for time or chronomodulated drug delivery system.

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance. However, there are certain conditions for Which such a release pattern is not suitable. These conditions demand release of drug after a lag time. In other words, it is required that the drug should not be released at all during the initial phase of dosage form administration. Such a release pattern is known as Chr DDS release. A Chr drug delivery system is characterized by a lag time that is an interval of no drug release followed by rapid drug release.

Table 1. Types of Biological Rhythms.

Period (τ)	Major rhythmic components
Short ($\tau < 0.5h$)	$0.1s < \tau < 1s$ $\tau \approx \text{min}$ Pulsatiles
Intermediate ($0.5h < \tau < 6 \text{ days}$)	Ultradian ($0.5h < \tau < 20h$) Circadian ($20h < \tau < 28h$) Infradian ($28h < \tau < 6 \text{ days}$)
Long ($\tau > 6 \text{ days}$)	Circaseptan ($\tau \approx 7 \text{ days}$) Circamensual ($\tau \approx 30 \text{ days}$) Circannual ($\tau \approx 1 \text{ year}$)

Table 2. VARIOUS CLASSES OF DRUGS USED FOR CHRONOTHERAPY

Class	Examples
Cardiovascular drugs	Verapamil, propranolol, diltiazem
Antiasthmatic drugs	Theophylline, albuterol, Terbutaline
Anticancer drugs	Cisplatin, doxorubicin, Methothrexate,
Anti Ulcer agents	Theophylline, albuterol, Terbutaline
Anticholesterolemic Agents	Lovastatin, simvastatin
Non steroidial anti-inflammatory Agents	Tenoxicam, ketoprofen, indomethacin,
Others	vitamin D3

Table 3. FDA approved ChrDDS in US market

Proprietary name;	Dosage form API	Chronopharmaceutical technology	Indication/rationale for Chronotherapy
Uniphyll® extended releasetablets	Theophylline	CONTIN	Asthma/increased bronchoconstriction in Morning
CoveraHS; extended Release tablets	Verapamil HCl	OROS®	Hypertension/increased BP in early morning.
Verelan® PM; extended release capsules	Verapamil HCl	CODAS®	Hypertension
Concerta® tablet	Methylphenidate HCl	OROS®	Anti-psychotic
Cardizem®LA; extended release tablets	Diltiazem HCl Verapamil HCl	CEFORM®	Hypertension

CLASSIFICATION OF CHRONOPHARMACEUTICAL DRUG DELIVERY SYSTEMS (CHRDDS) [1,3,8,9,10]

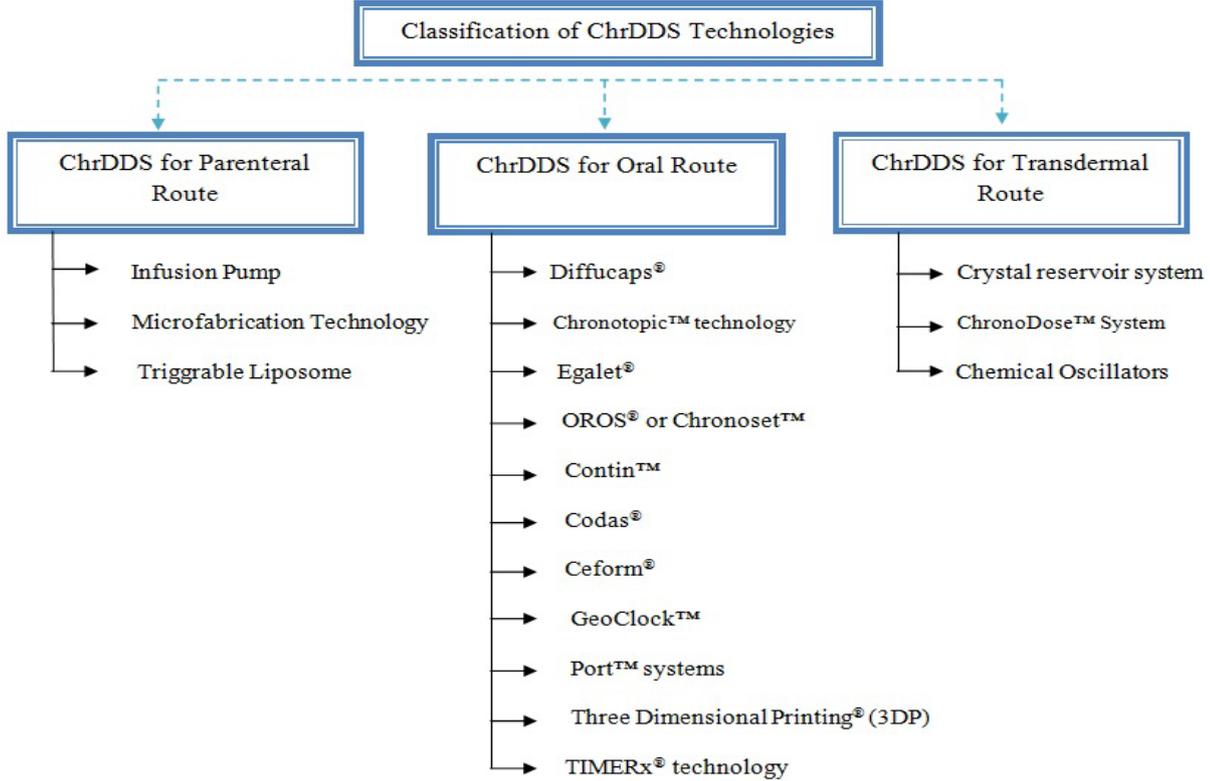


Fig. 1. OS Technology Chronopharmaceutical Drug Delivery Systems for Oral Route (8,11)

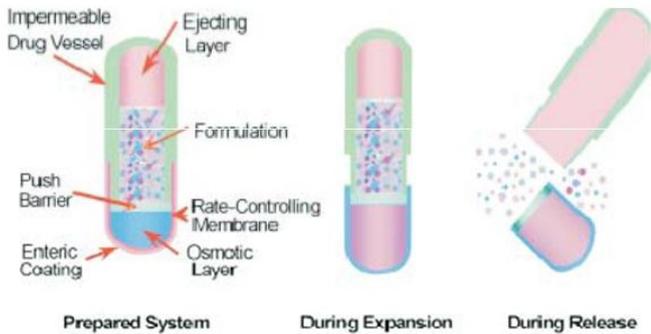


Fig. 3. Chronotopic Technology

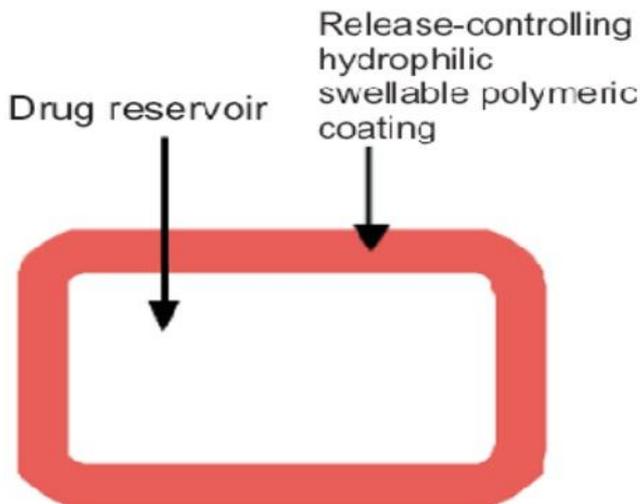


Fig. 2. Diffucap

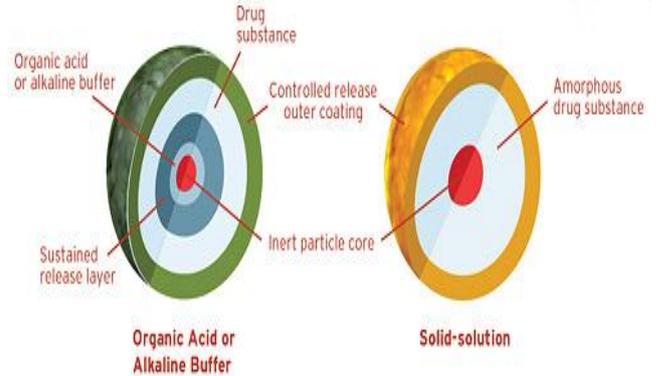


Figure 4. Port Technology

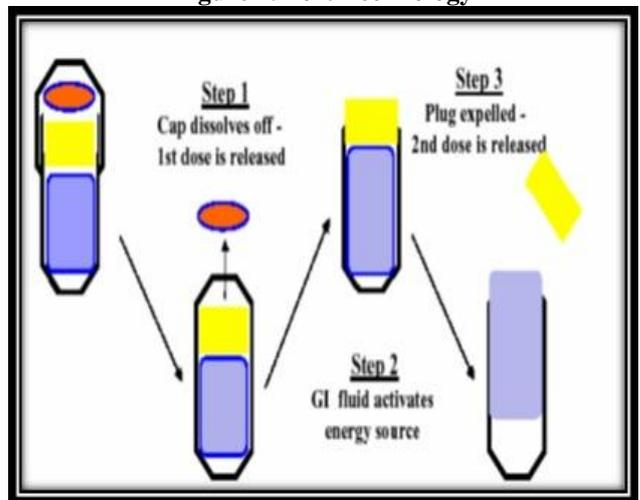


Fig 5. 24-hr clock diagram of the peak time of selected human circadian Rhythm with reference to the day-night cycle

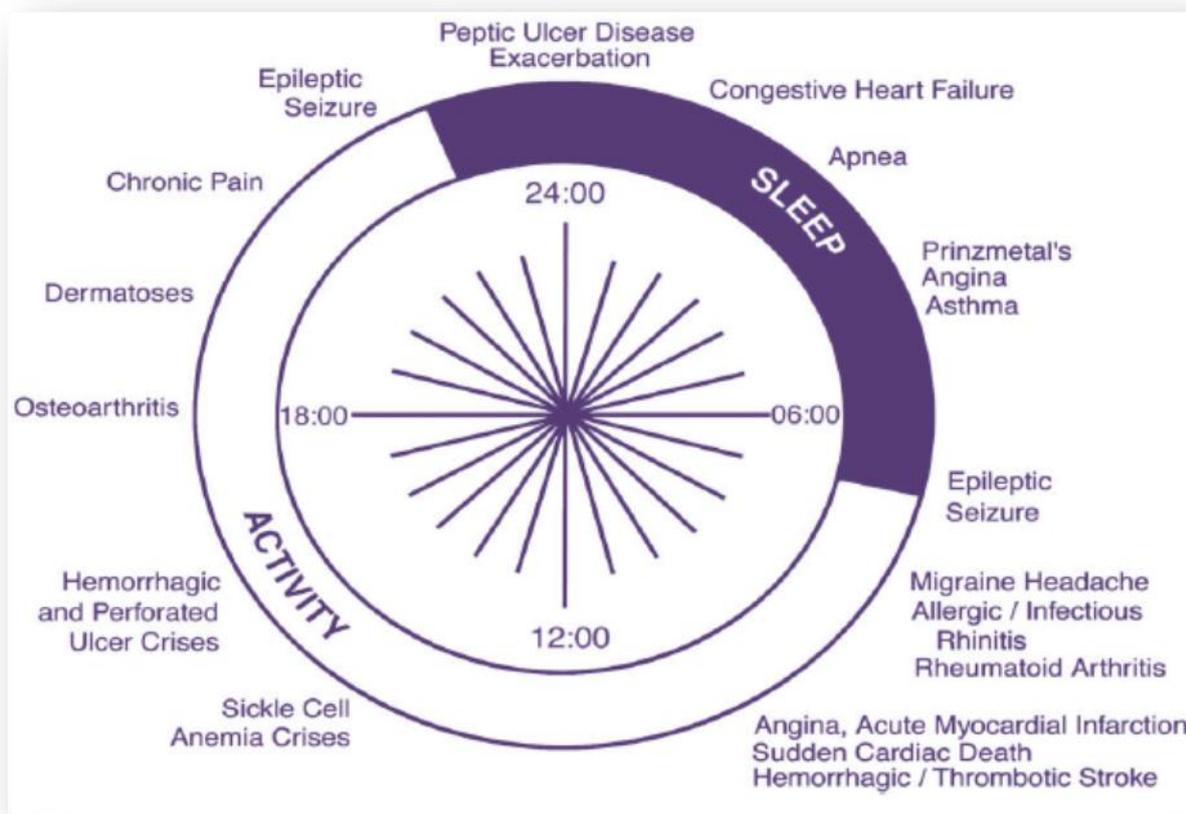
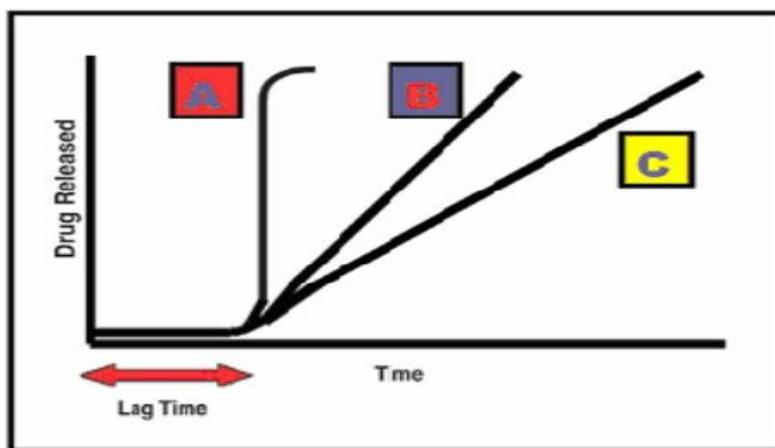


Figure 6. Drug release profile of ChrDDs (5,6)



A: Ideal sigmoidal release B & C: Delayed release after initial lag time

CONCLUSION

Advances in chronobiology and chronopharmacology has demonstrated the importance of biological rhythms in treatment of disease and this has led to a new approach to the development of novel drug delivery system-ChrDDS (Chronotherapeutical Drug Delivery System). As timing of drug administration in disease therapy has significant impact upon treatment success, ChrDDS in future is certainly going to gain popularity. Chronopharmaceutics will certainly improve patient outcome and optimize disease management in the

future. Research in chronopharmacology has demonstrated the importance of biological rhythms in drug therapy and this has led to a new approach to the development of drug delivery systems. Different technologies have been applied to develop time-controlled, pulsed, triggered and programmed drug delivery devices in recent years. Since it is seems that timing of drug administration in disease therapy has significant impact upon treatment success, chronotherapeutics remains an important area for continuing research.

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