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## A Review on Chronopharmaceutical Drug Delivery System

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### ABSTRACT

The Chronopharmaceutical Drug Delivery System (CDDS) has emerged during the last decade as a possible drug delivery system against several diseases, which may lead to the creation of a sub-discipline of pharmaceuticals to be explored called 'chronopharmaceutics'[1]. The review addresses the approaches to this sub-discipline, calls attention to potential disease-targets, and identifies existing technologies, hurdles and future of chronopharmaceutics. Chronopharmaceutics coupled with nanotechnology could be the future of DDS, and lead to safer and more efficient disease therapy in the future

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## INTRODUCTION

All functions in man are highly organized in time as biological rhythms of diverse periods, both in health and in disease. This represents a challenge for those involved in the development of drug-delivery systems to make possible the treatment of illness according to these physiological biological rhythms as a means of improving therapeutic outcomes [2]. Pharmaceutical companies are experiencing obstacles in discovering new medications that represent significant advances in the treatment of disease.

Drugs for several diseases are still given without regard to the time of the day. Variation in dosing time is generally related with the effectiveness and toxicity of many drugs. On the other hand, several drugs affect the circadian clock. The knowledge of interactions between the circadian clock and drugs is valuable in clinical practice. The pharmacodynamics and pharmacokinetics of the medication influence the chronopharmacological phenomena and recent advances in it have made the traditional goal of pharmaceutics rather outdated. With new advances in chronopharmaceutical medicine, there is reason to believe that staggering drug release times can have increased effectiveness on cancer patients compared to administering multiple drugs simultaneously.

Chronopharmaceutics has been described as a branch of pharmaceutics devoted to the design and evaluation of drug delivery system that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy[3].

Chronotherapeutics takes into account predictable administration-timedependent variation in the pharmacokinetics [4]of drugs as well as the susceptibility of target tissues due to temporal organization of physiochemical processes and functions of the body as circadian and other rhythms.

One approach to increase the efficiency of pharmacotherapy is the administration of drugs at times at which they are most effective and best tolerated. The chronotherapy of a medication may be accomplished by the appropriate timing of conventionally formulated tablets and capsules, and a special drug delivery system to synchronize drug concentrations to rhythms in disease activity[5]. The concept of chronotherapeutics is not new; the roots of clinical chronobiology date back to 1814, when Joseph Virey empirically recommended that opium should be dosed late in the evening, rather than in the morning. In the last few years recognition of the importance of the circadian rhythm to the health sciences has increased significantly.

In fact the human circadian time structure presents peaks of actions directly related to the daily routine of most human beings. As human physiology and biochemistry predictably vary during a 24 hour period it is easy to understand that some medical conditions present prevalence at certain periods of the day. The peak in serum cortisol, aldosterone, testosterone, platelet adhesiveness, blood viscosity and NK-cell activity is observed during the initial hours of daytime. Hematocrit is greatest and airway caliber (FEV1) best around the middle and afternoon hours, respectively.

Insulin, cholesterol, triglycerides, platelet numbers, and uric acid peak later during the day and evening. The rhythms of basal gastric acid secretion, white blood cells (WBC), lymphocytes, prolactin, melatonin, eosinophils, adrenal corticotrophic hormone (ACTH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) shows a peak at specific times during the nighttime. 24 hour rhythms in the processes that make up the pathophysiology of diseases cause prominent day-night patterns in the manifestation and severity of many medical conditions. The onset of migraine headache is most frequent in the morning around the time of awakening from nighttime. The sneezing and runny nose in allergic and infectious rhinitis is worst in the morning upon arising from nighttime. The symptoms of rheumatoid arthritis are worst when awaking from nighttime, while those of osteoarthritis are worst later in the day. The morbid and mortal events of myocardial infarction are greatest during the initial hours of daytime. The incidence of thrombotic and hemorrhagic stroke is greatest in the morning around the time of commencing diurnal activity. Ischemic events, chest pain, and ST-segment depression of angina are strongest during the initial three to four hours of daytime. Pain and gastric distress at the onset and acute exacerbation of peptic ulcer disease are most likely in the late evening and early morning.

The circadian period of blood pressure is a challenge for sustained delivery systems, as blood pressure may be lowered excessively during certain times due to the zero order drug delivery provided by the system[6]. Chronopharmaceutics address this limitation by delivering drug in concentration that varies according to the body's circadian rhythms. In this way it is possible to reduce blood pressure at the times where patients are at highest risk for cardiovascular events without excessive reduction during low periods. Circadian changes can also be observed in lung function and affect disease like asthma. It has been demonstrated that airway resistance increase progressively at night in asthmatic patients. Since broncho-constriction and exacerbation of symptoms vary during the day, asthma is well suited for chronotherapy, namely with beta 2- agonists and oral corticosteroids [7].

Also glucose and insulin levels' circadian variation have been studied and their clinical importance acknowledged [8].

Since the goal of insulin therapy is to mimic the normal physiologic patter of endogenous insulin in healthy individuals, chronotherapeutics seems an obvious path for insulin substitution therapies.

Chemotherapy has also been reported as being more effective and less toxic when drugs are administered at selected times that take advantage of tumour cell cycles.

The blood flow to tumours and tumour cell cycles. The blood flow to tumours and tumour growth rate are much higher during day activity phase than during the daily rest phase [9]. Clinical studies that determine the times at which effects are higher with lower undesirable side effects are of great importance to establish new drug regimens. Chronopharmaceutics also plays a major role at pain control therapies.

Many scientists are convinced that pain intensity is rarely constant over a 24 hours period. The daily pain profile must be used to determine the best time to administer an

analgesic drug to a patient. The time dependent rhythms in pain intensity depend on the medical conditions present. Morning pain is found in patients with angina pectoris, myocardial infarction, migraine, tooth ache and arthritis rheumatoid whereas nighttime's pain is more common in arthritic pain, gastro-oesophageal reflux and renal colic. In many other solutions as hypercholesterolemia, in some neurological diseases (mainly those related to nor adrenaline levels), in duodenal ulcers and gastrointestinal tract diseases chronotherapy can be used as a great tool to optimize the drug regimen, thus increasing the efficiency of treatment[10].

### **Marketed Systems**

Various systems have been developed taking chronopharmaceutics in consideration. Systems like CONTIN<sup>®</sup>, OROS<sup>®</sup>, CODAS<sup>®</sup>, CEFORM<sup>®</sup>, DIFFUCAPS<sup>®</sup>, and TIMERx<sup>®</sup> have been proposed. The use of hydrophilic matrixes is also very promising as release can be tailored to achieve the desired release programs without the need of specific industrial machines; the GEOMATRIX<sup>®</sup> is good example. More complex strategies can include the use of microchips in controlled release systems in order to obtain a determined release program. Hydrogels, namely stimuli-sensitive –hydrogels and temperature sensitive hydrogels have been reviewed as interesting drug delivery technology for chronopharmaceutics [11]. Chronopharmaceutics certainly seems to hold the potential to improve patient outcomes and optimize disease management in the future [12]. The selection of appropriate technology will have to take in consideration factor as the application range, ease of manufacture, cost-effectiveness and flexibility of the desired pharmacokinetic profile. Recognition of the importance of rhythms, especially circadian (24-hour) rhythms, to physiology, pharmacology, molecular biology, and the health sciences has increased rapidly over the past few years. It is now well established that all living creatures are endowed with biological clocks that orchestrate, during the 24 h and other time periods, all of life's processes and functions at every level of organization.

### **Chronopharmaceutical technologies**

Many technologies have been developed to deliver the drugs to the body according to the biological rhythm of the disease. The technologies developed to achieve this aim are described below. The formulations that have been approved by US-FDA for chronotherapy of the diseases and the technologies used are given in Table 1.

**Table 1. Chronopharmaceutical systems approved by US-FDA**

Indication/rationale for chronotherapy	Chronopharmaceutical technology	Proprietary Name; Dosage Form	API	Date of FDA approval
Asthma/increased bronchoconstriction in morning	CONTIN	Uniphyll®; extended release tablets	Theophylline	Sept 01, 1982
Ulcer/increased gastric acid secretion in evening	Physico-chemical modification of API	Pepcid® tablets	Famotidine	Oct 15, 1986
Hypercholesterolemia/increased cholesterol synthesis overnight	Physico-chemical modification of API	Zocor® tablets	Simvastatin	Dec 23, 1991
Hypertension increased BP in early morning	OROS	Covera HS; extended release tablets	Verapamil HCl	Feb 26, 1996
Hypertension	CODAS	Verelan® PM; extended release capsules	Verapamil HCl	Nov 25, 1998
Anti-psychotic	OROS	Concerta® tablet	Methylphenidate HCl	Aug 1, 2000
Hypertension	CEFORM	Cardizem LA; Extended release tablets	Diltiazem HCl Verapamil HCl	Feb 06, 2003
Hypertension	DIFFUCAPS	Innopran XL; extended release capsules	Propranolol HCl Verapamil HCl	Mar 12, 2003
Schizophrenia	OROS	Invega	Paliperidone	Dec 19, 2006

### CHRONOTOPIC® technology

It is also described in system with erodible, soluble or rupturable membrane system. It is basically 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.

### CONTIN® technology

In this technology, molecular coordination complexes are formed between a cellulose polymer and a 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 since it has a uniform porosity (semi-permeable matrixes) which may be varied [13]. This

technology has concretely enabled the development of tablet forms of sustained-release aminophylline, theophylline, morphine, and other drugs. Research suggested that evening administration of UniphyllR (anhydrous theophylline) tablets represented a rational dosing schedule for patients with asthma who often exhibit increased bronchoconstriction in the morning. Patients demonstrated improved pulmonary function in the morning compared with use of twice-daily theophylline when once-daily UniphyllR was administered in the evening. Thus, evening administration of once-daily theophylline may block the morning dip in lung function commonly seen [14]. CONTIN 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[15-16].

### **Physico-chemical modification of the API**

In this strategy, a proprietary method is used to modify the physicochemical properties (e.g. solubility, partition coefficient, membrane permeability, etc.) of the API to achieve the chronopharmaceutical objective. The rationale for such approach is based on the published work demonstrating that solubility and permeability are critical factors governing drug bioavailability [17]. Typical examples of the use of this strategy in chronotherapy are those of antihyperlipidemic statins (HMG-CoA reductase inhibitors) [18-19] and antiulcerative agents (histamine H<sub>2</sub> receptor-antagonists) [20-22].

### **OROS® 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 [23]. It is 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 another osmotically active agent. Upon contact with gastrointestinal fluid, this osmotic agent changes its characteristic from non-dispensable to dispensable viscosity. As a result active pharmaceutical is pushed away through the channel due to pump effect of the osmotic agent. It is used generally for designing of extended release tablet.

### **CODAS® technology**

Chronotherapeutic Oral Drug Absorption System (CODAS) technology is a multiparticulate system designed for bedtime dosing. Here nonenteric coating is applied on drug-loaded beads to delay the release of drug up to 5 h. Here release controlling contains mixture of both water-soluble and water-insoluble polymers. When this dosage form comes in contact with GI fluid water-soluble polymer gets dissolved slowly and pores are formed on the coating layer. Drug diffuses through these resulting pores. Water-insoluble polymer acting as a barrier maintains the controlled release fashion like release of verapamil [24]. The rate of release is independent of pH, posture and food.

### **CEFORM® technology**

The CEFORM<sup>®</sup> technology [25] allows the production of uniformly sized and shaped microspheres of pharmaceutical compounds. This ChrDDS approach is based on 'melt-spinning', which means subjecting solid feedstock i.e. biodegradable polymer/ bioactive agents combinations to the combination of temperature, thermal gradients, mechanical forces, flow, and flow rates during processing. The microspheres obtained are almost perfectly spherical, with a diameter typically ranging between 150-180  $\mu\text{m}$  and allow high drug loading. 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 either with an enteric coating or combined into a fast/ slow release combination. This technology has been actually used to develop CardizemR LA, 1-day diltiazem formulation as chronotherapeutic drug delivery system.

### **EGALET<sup>®</sup> technology**

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 [26]. Time taken to erode the inert plugs determines the lag time. The shells are made of slowly biodegradable polymers (e.g. ethyl cellulose) and plasticizers (such as cetostearyl alcohol), while the matrix of the plugs is a mixture of pharmaceutical excipients including polymers like polyethylene oxide (PEO).

### **DIFFUCAPS<sup>®</sup> technology**

This technology is nothing but capsule based system containing one or more drug-containing particles (e.g. beads, pellets, granules etc.). Each bead shows pre-programmed rapid or sustained release profile with or without lag time. It has been already discussed in system with erodible, soluble or rupturable membrane section.

### **Chronomodulating infusion pumps**

These infusion pumps are of light weights and high precision values in drug delivery [27]. Implantable infusion pump containing insulin is placed surgically within the subcutaneous tissue of the abdomen in the left upper or lower quadrant (above or below the belt). A catheter leads from the pump through the muscle layers into the peritoneal cavity where it floats freely and insulin delivery is by intraperitoneal route. It is refilled once a month or every 3 months by inserting a needle through the skin into the pump under physician's observation.

### **TIMERx<sup>®</sup> technology**

It is hydrogel based controlled release device. This technology can provide from zero order to chronotherapeutic release [28]. It can provide different release kinetic by manipulating molecular interactions. It has been claimed that the 'molecular engine' replaces the need for complex processing or novel excipients and allows desired drug

release profiles to be 'factory set' following a simple formulation development process. Basically, this technology combines primarily 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.

### **Three-dimensional printing®**

Three dimensional printing (3DP) is a novel technique used in the fabrication of complex oral dosage delivery pharmaceuticals based on solid free form fabrication methods. It is possible to engineer devices with complicated internal geometries, varying densities, diffusivities, and chemicals [29]. 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 pulses of about 4 h. This technology is the basis of the TheriFormR technology. The latter is a micro fabrication process that works a manner very similar to an 'ink-jet' printer. It is a fully integrated computer-aided development and manufacturing process. Products may be designed on a computer screen as three-dimensional models before actual implementation of their preparation process. This versatile technology may found potential application in chronopharmaceutics in the future.

### **Other controlled-release erodible polymers**

Erodible polymers have been designed in different forms (e.g. tablets, capsules, microparticles) for chronotherapeutic applications. For example, Ross et al [30] reported the development of a chrono-pharmaceutical capsule drug delivery system. The drug formulation is sealed inside the insoluble capsule body by an erodible tablet (ET) that is composed of an insoluble (dibasic calcium phosphate) and gel-forming excipient such as hydroxypropyl methyl cellulose. The time-delayed release of a model drug (propranolol HCl) was investigated by dissolution testing. Both composition and weight of ET influence the time of drug release rate. Programmable pulsatile release has been achieved from a capsule device over a 2–12 h period, consistent with the demands of chronopharmaceutic drug delivery. Guar gum-based matrix tablets represent a simple and economical alternative to existing drug sustained release dosage forms [31]. Eudragit RRL and RS 30D are pseudolatexes based on cationic copolymers stabilized with quaternary ammonium groups. An ionic buffer species and not the pH had a significant effect on the hydration and hence on the drug release from beads coated with these cationic polymers [32]. Recently, such polymers have been used in combination with biodegradable polymers to control the release of heparin for potential chronotherapeutic application against thrombosis and hypertension [33-34]. The rationale for chronotherapy against thrombosis is based on evidences that blood coagulability follows a circadian cycle. An excellent review of pulsatile drug-delivery system involving erodible polymers has been made by Bussemer et al [16–35]. By careful selection and combination of polymeric drug carrier of different

erosion/ degradation kinetics, or by manipulating the interaction energy between the drug and the polymer, it may be possible to control the release of a drug at a rate that matches the requirement of the biological rhythm of a given disease state.

### **Controlled-release microchip**

An alternative method to achieve pulsatile or chronopharmaceutical drug release involves using micro fabrication technology. Santini et al [36] reported a solid-state silicon microchip that can provide controlled release of single or multiple chemical substances on demand. The release mechanism was based on the electrochemical dissolution of thin anode membranes covering microreservoirs filled with chemicals in solid, liquid or gel form. Pulsatile release of heparin, human growth hormone and radiolabeled dextran from Poly(L-lactic acid) and poly (D,L-lactic-co-glycolic acid) membranes have been reported.<sup>105</sup> This technology has the potential to be used in the design of chronotherapeutic delivery system with a better control over drug release kinetics to match biological requirement over a period of time.

### **GeoClock® technology**

The concept is designed on the basis of Geomatrix technology [37]. 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 presence of dissolution medium the barrier layer swells and becomes gel. This gelling layer is not eroded but acts as a modulating membrane to control release process. The erodible surface is instead progressively removed by the dissolution medium. Upon erosion more planar surface(s) of the active core is exposed with increasing time to outer environment which helps drug release.

### **PORT® technology**

The Programmable Oral Release Technologies (PORT) system is a uniquely coated, encapsulated system that can provide multiple programmed release of drug [26]. It contains a polymeric core coated with a semi-permeable, rate-controlling polymer. Poorly soluble drugs can be coated with solubilizing agents to ensure uniform controlled release from the dosage form. In capsule form had gelatin capsule is coated with a semi-permeable, rate-controlling polymer. Active medicament mixed with osmotic agent is kept inside capsule shell. A water-insoluble plug is used to seal the capsule shell. Immediate release compartment can be added according to need.

## **CONCLUSION**

A major progress has been achieved towards chronopharmaceutical drug delivery systems that can effectively treat disease with non-immediate dosing therapies such as diabetes. Products that are currently under development for commercialization are for the delivery of proteins, hormones, pain medications and other pharmaceutical compounds. The key considerations in the design of polymer based pulsatile systems are the biocompatibility and the toxicity of the polymers used, response to the external stimuli,

the ability to maintain the desired levels of drugs in serum, the shelf life and reproducibility. Besides, the body's biological time's structure must be counted and respected in the designing of pulsatile drug delivery system for neuropeptides, hormone, cytokines or other agents that act upon oscillating system. By selecting optimal time to achieve the desired effect, treatment opportunities may arise and undesired side effects can be minimized. These considerations, coupled with the potential therapeutic benefits of pulsatile drug delivery systems, should ensure that the current high level of interest in this would extend well in to future and it will represent a milestone in drug delivery system

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