Chrono Modulated Therapy-A Review

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ABSTRACT

Chrono therapeutic drug delivery systems stay attaining prominence in the area of pharmaceuticals. It decreases dosing incidence, toxicity, and distributes a drug that matches the circadian rhythm of that definite disease when the signs are exciting to sorrier. ChrDDS is the essentially time-controlled drug delivery system. It offers a patient with a staggered profile of the therapeutic agent. It makes some consecutive changes in the ADME process. This mechanism is lag time independent of environmental variables including pH, enzymes, gastrointestinal motility. The circadian rhythm regulates many body functions in humans, such as metabolism, behaviour, sleep patterns, and hormone production. Chronotherapy has gained attention as a novel and rational approach to exploit the best. Presently, drugs are delivered in a controlled release like an IR, ER, & PR. Certain conditions that follow circadian rhythms include hypertension, diabetes, cardiovascular, asthma, neurological disorders, ulcer conditions, etc. 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 are Diffucaps, OROS, Codas, 3D printing, Egalet, Port, etc. this system is designed according to body-clock. Special drug delivery technology must be relied upon to synchronize drug concentrations to rhythms in disease activity with the body’s 24-hour rhythms to extend therapeutic effectiveness and reduce/avoid side effects. In this article, the various concepts like a mechanism of circadian rhythms, current obstacles to the production of chronopharmaceutical drug, circadian chronotherapy in various diseases, a profile of launched Chronopharmaceutical dosage forms, various technologies for systemic delivery, chronopathalogy have been reviewed.

INTRODUCTION

CHRONOPHARMACEUTICS: Chronopharmaceutics comprises of twofold: Chronobiology & Pharmaceutics. Chronobiology is analyses the biological rhythms and their mechanisms.

ChrDDS formulated to deliver the drug to match the timings of the disease. The delivery of drugs can be done either after a lag-phase or can be sustained release (Sharma et al., 2018). These systems are used to define a kind of drug formulation which
can cause circadian variation in drug plasma levels (Sajan et al., 2009). Chronotherapy is a novel system which provides a time lag at altered release rates and it may be attained by stimuli-sensitive and pulsatile drug delivery systems (Ashwini et al., 2011). It fulfills the criteria of drug delivery at a specific time as per the pathophysiological need of the disease also it improves patient compliance (Nainwal, 2012). Chronotherapy deals with the circadian rhythm of few diseases, as stated in Table 1.

The efficiency and toxicity of many drugs vary depending on the relationship between the dosing schedule and the 24 hr rhythms of biochemical, physiological and behavioural processes (Ohdo, 2010).

Chronotherapeutics refers to a scientific approach in synchronizing drug delivery in a modus consistent with the body’s circadian rhythm, including disease states to produce maximum health benefit and minimum harm.

There are three sorts of mechanical rhythms in our body, they are:

1. Circadian: Circa(about) & dies(day).
2. Ultradian Oscillation (more than one cycle per 24 hrs).
3. Infradian Oscillations those are lengthier than 24 h (less than one cycle per day) (Shidhaye et al., 2012).

A self-sustaining oscillation of endogenous origin is a biological rhythm. It is specified by time, degree, amplitude and phase characteristics. The Circadian Time Structure, as shown in Figure 1.

1. The period is the span of time taken to complete a single cycle.
2. The level is the starting point around which rhythmic variation takes place.
3. Most circadian rhythms can also vary in amplitude with changes in health status.
4. Phase refers to the clocking of particular characteristics, such as peak and trough values, with a rhythm related to the time scale (Smolensky and Peppas, 2007).

Chronopharmacodynamics is the area of research that examines the circadian change in the mode of action of the medicine and matches administration to achieve optimal pharmacodynamic response in the circadian cycle for a particular medicine (Kaur et al., 2016). In the very aggressive health issues, periodic sequencing of treatments can also play a role in patient survival. The perception of chronotherapeutics – timing medication to a biological need to enhance beneficial outcomes or to reduce or eliminate adverse effects – is not a novel one (Smolensky and Peppas, 2007).

Ultimate features for ChrDDS should

1. In parenteral administration, it Should be biocompatible and biodegradable.
2. Non-toxic with the treatment of ChrDDS.
3. Have a feed-back control system(e.g., self-regulated, the adaptive capability to circadian rhythm and the individual patient to differentiate between awake-sleep status).
4. Self-controlled and adaptive ability to circadian rhythms.
5. It should be economical for manufacture (Shanmugan, 2015).

In response to changes in the pH, ionic strength, or temperature of the contiguous fluid, they may display extreme ups and downs in their swelling behaviour, network structure, permeability or mechanical strength. Other hydrogels are capable of reacting to electric or magnetic fields or to changes in the concentration of glucose. These hydrogels can be used in a wide range of applications due to these particular characteristics, such as separation membranes, biosensors, artificial muscles, chemical valves, and drug delivery systems. The most widely studied temperature-sensitive hydrogel was crosslinked poly(N-Iso propyl acrylamide) (PNIPAAm).

Recent work towards that eventual target included the consumption of organic oscillators (pH & stimuli-sensitive polymers) (Youan, 2010).

Current obstacles to the production of chronopharmaceutical drugs: It requires developments in

1. Biomaterials of rhythm
2. Development of rhythms & models
3. Governing instructions relating to these kinds of enhanced types of dosage.

**Biomaterials of rhythm and Structure plan**

Based on lessons learned from the environment, some biomaterials have been developed to counter peripheral provocations such as temperature, pH,
light, electrical field, chemicals and ion strength. These approaches are basically drastic changes in one of the following: structure, the appearance of the surface, solubility & development of complex molecular self-assembly or transformation from sol-to-gel.

**Development of rhythms & models**

Other major obstacle to the formulation of chronopharmaceutical drugs is certainly need to build rhythm and use reliable models, not just to anticipate these various delivery mechanisms to have complex physicochemical properties, but also their physiological changes. Simulations are also necessary to know evolution. Mathematical models have been seen in universal rhythmic systems, like a lot of physical activities.

**Governing instructions relating to these kinds of enhanced types of dosage**

In any mortal activity, it is continuously advisable, to begin with, a focus in the end. If chronopharmaceutical manufactured goods are tossed onto the flea market and widely recycled in experimental preparation, the attention of modern supervisory barriers must be maintained. The regulatory difficulties include before and after-consent deliberations.

In pre-approval segment, it is occasionally problematic to determine chronotherapeutic benefit in CR or MR designs in the medical background. This is partially due to the first two obstacles, namely the absence of genuinely rhythmic biomaterials and drug delivery systems and rhythm engineering and enhanced predictive methods (Patel et al., 2013).

The drug’s well-being and productivity are accomplished by harmonising the drug’s ultimate plasma absorption with the body’s circadian rhythm. Profile of Chronopharmaceutical dosage forms launched are given in Table 2 (Ashwini et al., 2011).

**Advantages**

1. Decreases adverse effects and better acceptability.
2. Reduced threat of tissue injury.
3. Zero chance of dumping the dose
4. The elasticity of nature.
5. The comfort of incorporating various compositions or discharge cycles
6. Developers sustainability.
7. Develops convenience and safety for patients
8. Implements a unique pattern of release.
9. It covers patent rights, globalises the brand and overcomes competition (Langer and Tirrell, 2004; Anderson, 2004).

**Disadvantages**

1. Limited loadings of medications.
2. A comparably greater desire for excipients.
3. Lack of reproducibility and effectiveness in development.
4. A wide variety of method variables.
5. Different formulation measures.
6. Lower production costs.
7. Necessity of innovative technologies.
8. Educated / eligible persons required for build-up (Patel et al., 2013).

**Chronotherapy in various Diseases**

Although our physique has an intrinsic 24-era sequence, in the same way, the circadian forms might also be monitored by some diseases, chronotherapy is very appropriate in the treatment of such types of diseases by controlling the dosage and the frequency of drug management conferred on the circadian rhythms. The following is the tilt of those diseases that can be healed more ominously by chronotherapy.

- High blood pressure, Bronchospasm, Ulcerative infections, Cardiac infringement, Arthritis, Hyperlipidemia, Cerebral vascular damages.

**Hypertension**

When we wake up in the morning, the heart rate and blood pressure will be high and it will start to decrease in the afternoon and at midnight, it hits the minimum. But the blood pressure in patients with hypertension upon waking is comparatively high. After waking up, systolic blood pressure increases up to 3mmHg/hour for 4-6 hours and diastolic myocardial ischemia occurs at sunrise.

**Bronchial asthma**

Due to the stress decrease in inspiratory muscle tone, decrease in pulmonary compliance, increased intrapulmonary blood pooling, which facilitates airway narrowing, the rise in resistance in asthmatics is much greater during sleep. The Rhythm of a Circadian is predominantly significant in accepting the degenerated ups and downs in lung function of asthmatics at night (Satyanarayana and Pavithra, 2015).
Table 1: A foremost objective of chronotherapy in the dealing of a few diseases

| Diseases                     | Circadian rhythm                                      |
|------------------------------|-------------------------------------------------------|
| Allergic Rhinitis            | Worse during the early hours, upon rising             |
| Asthma                       | Exacerbation is more normal during the sleep cycle   |
| Rheumatoid Arthritis         | More frequent symptoms during the sleep cycle        |
| Osteoarthritis               | Worse signs in the middle / later part of the day     |
| hepatic encephalopathy       | Chest pain and ECG shifts are more intense at an initial stages. |
| Cardiac Infarction           | The highest occurrence in the early morning           |
| Stroke                       | The higher prevalence in the morning                  |
| Coronary heart fatality      | Higher occurrence in the morning after waking up      |
| Disease of Peptic Ulcer      | Worse, late at night and in early morning             |

Table 2: Profile of Chronopharmaceutical dosage forms launched

| Proprietary list | Active pharmaceutical ingredient | Innovation in Chronopharmaceutics | Method of release profile |
|------------------|----------------------------------|-----------------------------------|---------------------------|
| UniphyllR        | Theophylline                      | CONTINR                           | Controlled release        |
| InnopranR XL     | β-blocker                         | DIFFUCAPS                         | Instant Liberation        |
| Covera-HSR       | Calciumchannel blocker            | Osmotic release oral system       | Osmotic regulation        |
| VerelanR PM      | Verapamil                         | CODAS                             | Rapid/sustained release   |
| InnopranR XL     | Verapamil                         | DIFFUCAPS                         | Osmotic regulation        |
| Pepcid           | Famotidine                        | API rheological modification      |                           |
| LipovasR         | Simvastatin                       | API rheological modification      |                           |
| InvegaTM         | Paliperidone                      | OROS                              | Swelling/diffusion/erosion|
| Glucotrol        | Glipizide                         | OROS                              |                           |
| Glicirid-MR30    | Gliclizide                        | Hydrophilic matrix technology     | Dual drug release         |
| KAPIDEXTM        | Dexlansoprazole                   | DDR Technology                    | Swelling/erosion          |
| Theirform        | Molsidomine                       | Geomatrix technology              | Delayed release           |
|                 | Rabeprazole                       | Enteric coating technology 3DP     | Immediate release/controlled release |

Figure 1: Circadian Time Structure
Peptic Ulcer Disease
Ulcer healing is directly linked to how much it prevents acid secretion during the night. Many medications used for this purpose are lipophilic and are observed to have a higher absorption rate in the early morning hours than any other time of day. Omeprazole when given only in B.D. and O.D. (evening dose) are important in prevention night symptoms (Satyanarayana and Pavithra, 2015).

Myocardial Infarction
The 34% events of myocardial infarction are taking place in the morning from 6 A.M till noon. Persistent Carbonic anhydrase inhibitor-2 can relieve pain effectively when taken at daybreak. Furosemide, when administered at night demonstrates a surge in the flow of urine, but increased depletion of Sodium ions, chloride ions within the first 60 minutes relative to the medication at night. After an evening injection, the rise in blood glucose deliberation is significant. Nominal benefit for ischaemic actions is during the pre-lunch hours for thrombolytics and heparin. Labetolol is more effective in handling the spike in blood pressure early in the morning (Satyanarayana and Pavithra, 2015).

Rheumatoid Arthritis
It is a severe chronic inflammatory condition with signs of stiffness, swelling and discomfort in one or more joints. The severity of these symptoms is three times higher between 8:00 a.m. and 11:00 a.m. Commonly prescribed NSAIDs such as flurbiprofen, ketoprofen, indomethacin at sleep time safeguard the tolerable process of daybreak alert of RA. In RA patients, aspirin, non-acetylated salicylates, and various other NSAIDs are used to alleviate joint swelling and restore function. Equal doses of aspirin and non-acetylated salicylates are anti-inflammatory in RA (Satyanarayana and Pavithra, 2015).

Cerebral vascular Damages
Cerebrovascular misfortunes are more prevalent at sunrise between 10 am and 12 pm and will be significantly reduced from sunrise to sunset. In these conditions, the main goal of chronotherapy is to administer the medication at higher doses in the morning and at a slightly lower dose at noon and at midnight. A number of ACE inhibitors, such as Atenolol, Nifedipine and Amolodipine, are often more active at night when administered.

Hyperlipidemia
The HMG CO-A inhibitors are recommended as morning doses after the understanding the circadian rhythms. The report was re-evaluated and the evening supplements were advised as the consumption of fatty acid and its biosynthesis is more in the abstaining state in the sundown hours.

Cancer chronopharmacology
Since cancer cells lose their internal timekeeper and divide more quickly than normal cells, cancer is considered a malfunctioning internal clock disease. The rhythms of circadian in

- Target tissues: tissues that are stable and cancerous;
- Chronopharmacology of drugs against cancer; and
- Chronotoxicity of anticancer drugs Studies indicates that normal cells and tumour cells have separate chronobiological cycles.
Circadian differences in animals and humans are subject to the metabolism, elimination and toxicity of these drugs. In addition, early diagnostic figures indicate that the effectiveness of anticancer chemotherapy could be improved by an optimal circadian schedule level (Satyanarayana and Pavithra, 2015).

**Chronobiology of Epidermis Ailments**

Cell regeneration explosion diverges close towards Thirty pleats in 24 hours, also with a maximum presence at nighttime but worst at noon. In the case of psoriasis, the cell proliferation rate of the skin affected is higher than average. In areas of psoriasis,

1. Cell proliferation rates are high-between 9 pm. and 3 am.

2. Cell proliferation rates are least at between 9 am and 11:00 am.

Cell proliferation in the dermis is maximal at 9:00 a.m. And at 03:00 a.m. The highest inflammatory activity happens at night and less in the morning (Satyanarayana and Pavithra, 2015).

**Diabetes Mellitus**

NIDDM Controlled treatment for elderly patients competing with one another. It is rapidly metabolized with oral medicine. Miglitol ahead of meals. Sulfonylureas 20-30 min before a meal, α - glucosidase inhibitors with food.

**Seizure disorder**

Convulsive seizures are maximum expected between 6-7 am. Gabapentin or other Anticonvulsant drugs for earlier wake up.

**Chronobiology of CNS disorder**

Rhythms are active throughout the level of subarachnoid receptors. This behaviour possibly relied on its impact on the function of cerebral pacemaker structures (Suprachiasmatic nuclei, hypothalamus and pineal gland) (Satyanarayana and Pavithra, 2015).

**Governing Apprehension**

While chronopharmaceutical formulations are more useful than traditional products, there are some technical difficulties, due to the fact that changed release formulations present specific challenges from conventional and integrated formulations which provide a more defined drug overview and a description for controlled release (Prevesh et al., 2013).

**Chronopharmaceutical delivery methods for systemic delivery**

The various chronopharmaceutical drug delivery system (CHRDDS) techniques are available which are depicted in Figure 2.

**Chronomodulating saline mechanism**

programmable Synchronomed®, Melodie®, Rhythmic® and the Panomat® V5 infusion pumps these can be used in the chronotherapy of many dis-ease conditions such as cancer and diabetes.

**Microfabrication Technology**

Controlled release microchip. It consists of a solid-state silicon microchip that can provide controlled release of drugs through an electrochemical dissolution of thin anode membranes by micro-reservoirs of solid, liquid or gel-shaped elements. Such type of techniques are used in diabetes, Parkinson’s disease, congestive heart failure (Reddy et al., 2013).

**CONCLUSION**

A very likely path for delivery systems are a novel therapeutic system. Entirely prolonged and regulated products produce an expected beneficial effect but fail in biological rhythm ailments. The bioavailability, effectiveness, and toxicity of the medication have been documented to change over a 24hr span. Circadian disorders such as asthma, osteoarthritis, RA, cholesterol synthesis, etc., need chronopharmacotherapy. In this review, how the human body circadian clock responds on various diseases & how the drugs will release in specified lag time. Chronotherapy might have all the prospects to become tomorrow’s endorsed, refined oncology concept without adding much more to the cost of existing therapy. Distinct pulsatile designs have been discovered and promoted, few technologies in various routes and their effects on the circadian rhythm of the various disease in specified time also discussed. Chronotherapy, which is likely to ensure a bright and huge future.

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**Conflict of Interest**

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