



CHRONOPHARMACEUTICS: A MODERNIZE TECHNIQUE OF DRUG DELIVERY SYSTEM

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ABSTRACT:

With the progression in the field of Chronobiology, modern drug delivery approaches have been raised to another idea of chronopharmacology. However, the major limited access in the improvement of drug delivery system that coordinate the circadian rhythm chronopharmaceutical drug delivery system (ChrDDS) might be the accessibility of proper innovation. The most recent decade has seen the rise of ChrDDS against a few illnesses. This review presents the idea of chronopharmaceutics, addresses hypothetical/formal ways to deal with this sub-discipline, underscores potential disease targets, returns to existing advances and instances of ChrDDS. Future improvement in chronopharmaceutics might be made at the interface of other developing techniques, for example, system biology and nanomedicine. The expanding research in ChrDDS may lead to the formation of another sub-discipline in pharmaceutics known as chronopharmaceutics.

KEY WORDS: Chronopharmaceutics, Chronotherapeutics, Circadian rhythm, Chronopharmaceutical technology, Chronopharmacology.

INTRODUCTION

Chronopharmaceutics has been described as a part of pharmaceutics dedicated to the structure and assessment of drug delivery system that relate a bioactive operator at a rhythm that preferably coordinates the biological requirement of a given disease treatment^[1]. Chronotherapeutics considers unsurprising time dependent variety in the pharmacokinetics of drug just as the susceptibility of target tissues because of association of physiochemical procedures and elements of the body as circadian and different rhythms^[2]. One way to deal with increment the efficacy of pharmacotherapy is the administration of medications at a time at which they are best effective and best tolerated.

The chronotherapy of a medicine might be practiced by the suitable planning of routinely defined tablets and capsules, and a unique drug delivery system^[3,4]. The idea of chronotherapeutics isn't new, the underlying foundations of clinical chronobiology go back to 1814, when Joseph Virey exactly prescribed that opium should be dosed late at night, rather than prescribing in the day^[5]. Over the most recent couple of years, the significance of the circadian rhythm to the health sciences has expanded fundamentally. In fact the human circadian time structure presents peak of activities identified with the everyday schedule of most people. As human physiology and biochemistry typically vary during a 24 hour time period, it is straightforward that some medical conditions present commonness at specific times of the day^[6].

An orderly timed circadian system implies that every function occurs at a specific moment in the temporal reference scale. Xenobiotics will have different effects as a function of the time of day they are given,



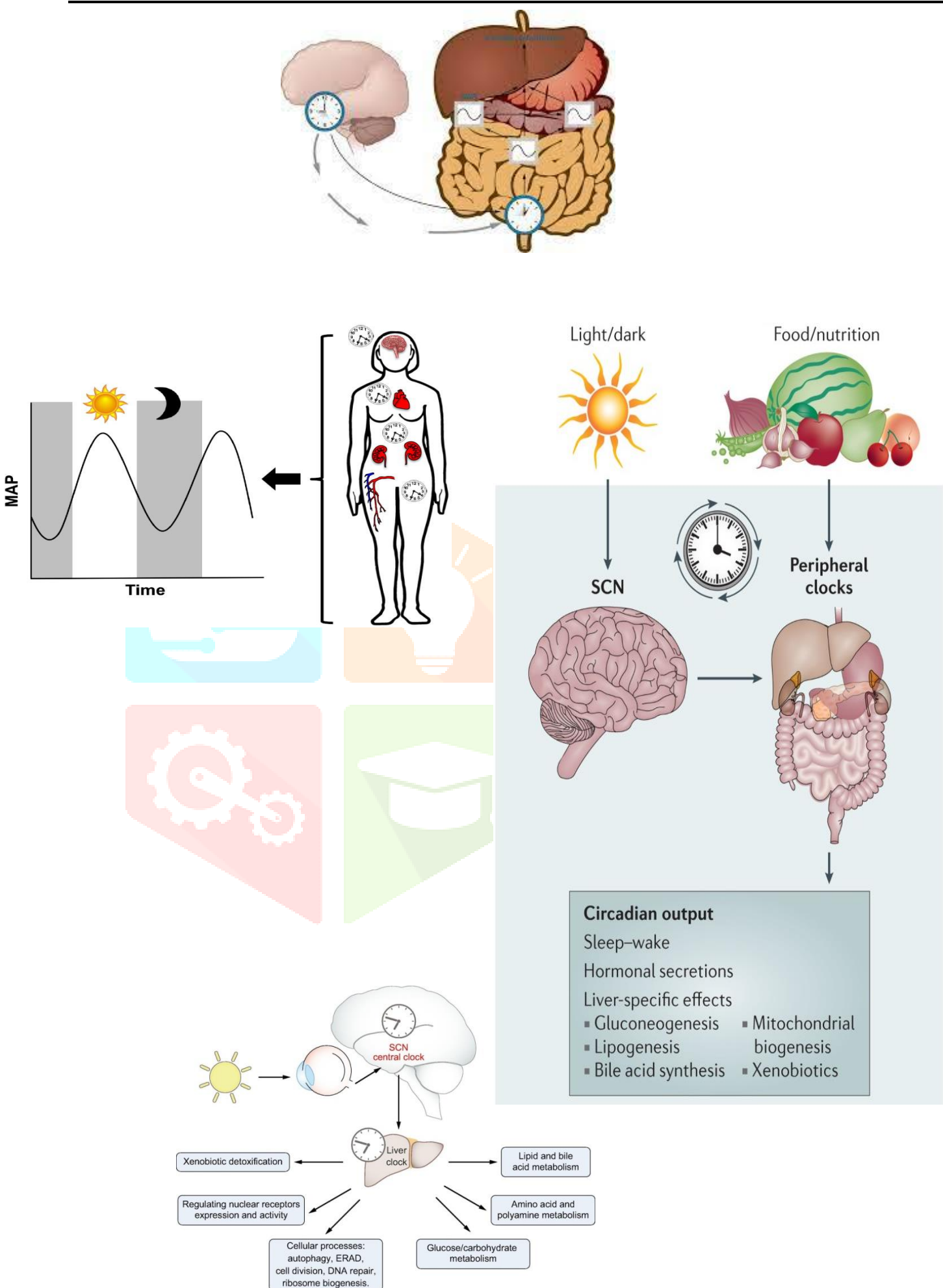
- Chronopathology describes the time-dependent effect of a pathological agent to cause the disease.
- Chronopharmacology describe the time-dependent variations in response to a pharmacological agent^[7].
- Chronotoxicology describes the daily changes in the activity of toxic agent on a given organism^[8].

That the activity of any pharmaceutical agent varies as a function of time of day of administration is in contradiction to the homeostatic principle that holds that a given agent will always produce the same effect providing that a constant concentration is kept in circulation. Administration of equal doses of a xenobiotic repetitive and equidistant during the day or the infusion to a constant rate, leads to the periodic variation in desired and undesired effects. A constant concentration of the xenobiotic in blood is not associated with constant effects along time.

HUMAN PHYSIOLOGICAL AND BIOCHEMICAL ACTIVITIES WITH RESPECT TO THE CIRCADIAN RHYTHM:

The rate of thrombotic and haemorrhagic stroke is most prominent toward the beginning of the day around the hour of initiating diurnal activity^[6]. Ischemic activity, chest pain, and ST-segment depression of angina are most grounded during the underlying three to four hours of daytime. The peak in serum cortisol, aldosterone, testosterone, platelet adhesiveness, blood viscosity and NK-cell movement is seen during the morning. Insulin, cholesterol, triglycerides, platelet numbers, and uric acid peak later during the day and night.

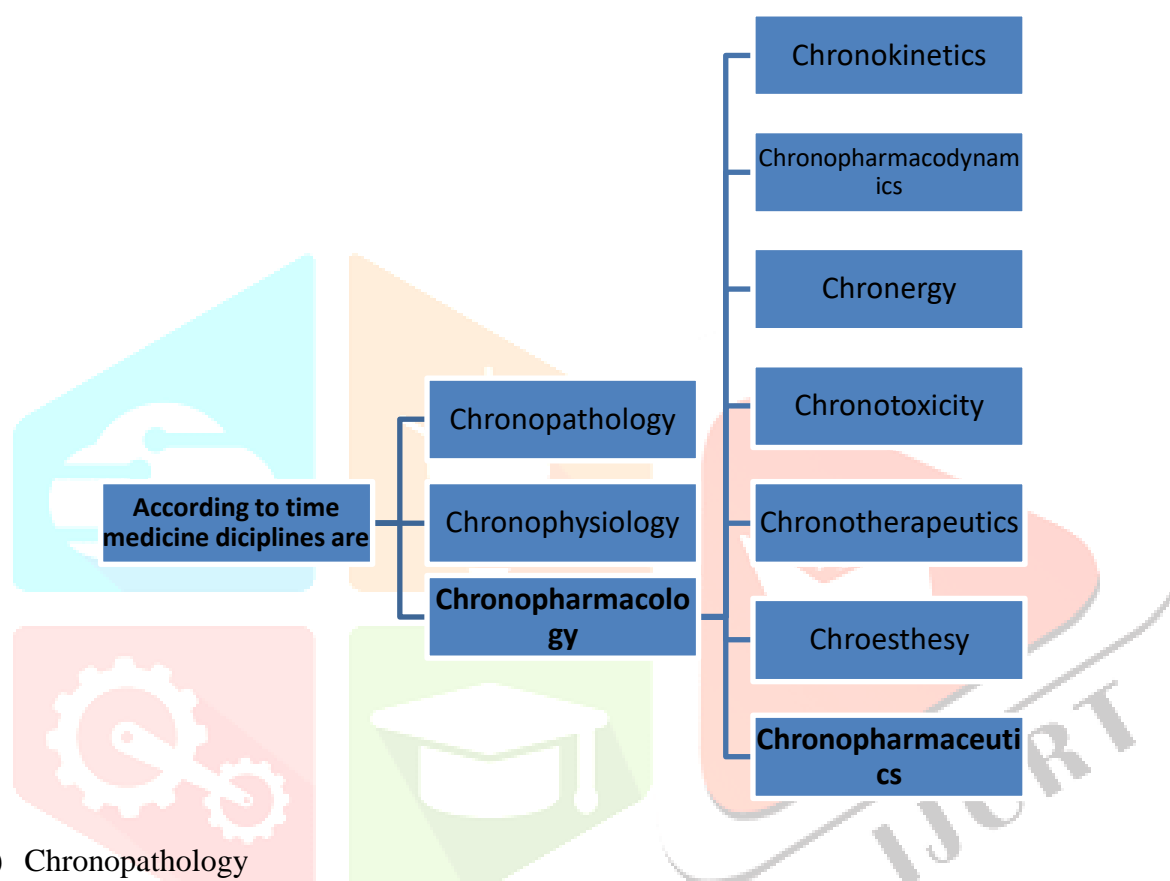
The rhythms of basal gastric acid secretion, white blood cells (WBC), lymphocytes, prolactin, melatonin, eosinophils, adrenal corticotrophic hormone (ACTH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) shows a top at the evening time^[9-11]. 24 hour rhythms in the procedures that make up the pathophysiology of disease cause prominent day-night pattern in the indication and seriousness of numerous diseases. The mortal events of myocardial infraction are most prominent during the morning periods of daytime. The beginning of headache migraine is generally visits in the first part of the day around the morning time.



The sneezing and runny nose in hypersensitive (allergic) and infectious rhinitis are most exceedingly terrible toward the beginning of the day^[12]. The symptoms of rheumatoid arthritis are most noticeably awful while getting up at night time, while those of osteoarthritis are most exceedingly awful later in the day. pain and gastric trouble at the beginning and acute peptic ulcer infection are in all likely occur in the late night and early morning. Epilepsy seizures are common around rest time especially at sleep and counterbalance in the first part of the day. The side effects of congestive cardiovascular failure are more worst at night. The danger of asthma attack is most during the night time^[13].

CLASSIFICATION

In consideration to time and medicine we can categorise the treatment in various manner,



1) Chronopathology

It describes alterations in biological temporal characteristics of organisms related to pathological state, such as Psychoses, Cancers, Ulcers and Blood pressure diseases.

2) Chronophysiology

It is a science that studies the physiological process with respect to time. (eg. Harmon secretion alternates the concentration throughout the day)

3) Chronopharmacology

It is a science concerned with pharmacological action of various drug over a biological timing.

a. Chronokinetics

Chronokinetics is the study of absorption, distribution, metabolism and excretion (ADME) of drug according to the time.

b. Chronopharmacodynamics

It deals with mechanism of time-related variation in effects and metabolism of drugs in healthy organism.

c. Chronergy

It is the study of changes of both desired (effectiveness) and undesired (toxicity, tolerance) effects on the organism as a whole.

d. Chronotoxicity

It refers to the change in organisms sensitivity to toxicants in with respect to time.

e. Chronotherapeutics

Medical treatment given according to the schedule that related to the person's biological clock, in order to maximize the health benefits and minimize adverse effects on person's life.

f. Chronesthesia

Chronesthesia is the rhythmic changes in susceptibility/sensitivity of the target system to a drug, which cannot be explained by chronokinetic changes.

g. Chronopharmaceutics

Chronopharmaceutics refers to a treatment method in which in-vivo drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effect.

SUSTAIN RELEASE SYSTEM^[14,15] :

Development for overcome of these problems mainly by the pharmaceutical industry during the last decades is as a formation of sustain release system.

The principal behind that is as follows:

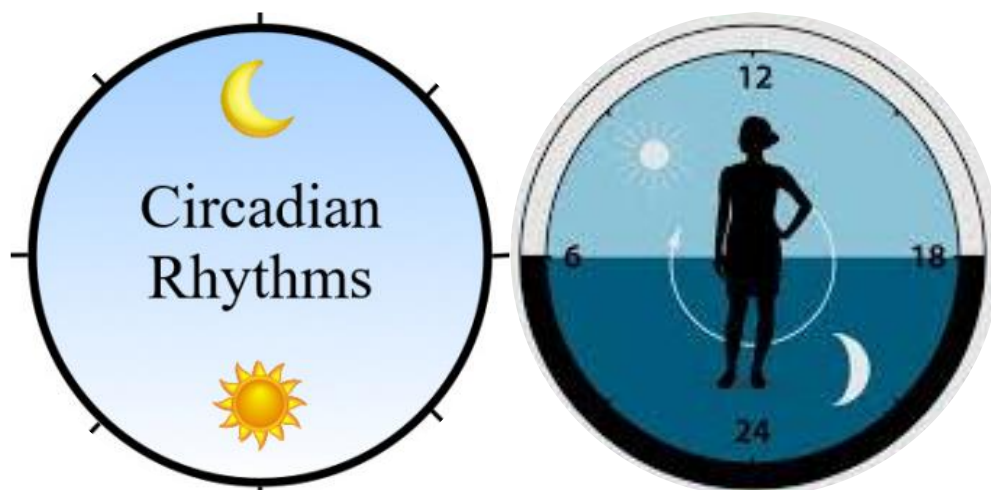
- (i) a more uniform plasma drug profile with fewer occasions when super or sub-therapeutic concentrations of the drug, or its active metabolite(s) occur;
- (ii) a smoother therapeutic response over the dosage interval (provided the time course of drug effects reflects the plasma concentration-time profile).

One of the objectives of these systems is to give zero order, constant rate, delivery of bioactive agents. The circadian rhythm additionally influences the drugs interaction with the body. Therefore the way that kinetics and dynamics of medications are straightforwardly influenced by biological rhythms and the time of drug administration is very important for the pharmacological effect. For certain diseases enough logical proof has been gathered so as to prescribe the utilization of chronotherapeutics rather than a conventional way of medication. For example, The role of chronotherapeutics in hypertension management is based on the recognition that blood pressure does not remain constant during the day, tending to be higher in the early morning and lower in the evening.

CHRONOPHARMACEUTICS :

Chronopharmaceutics might be considered as an connection between the current ideas of chronobiology, chronopharmacology, chronopharmacokinetics, chronotherapeutics and chronotoxicology^[16]. To know the idea of chronopharmaceutics, it is essential to know the ideas of chronobiology and pharmaceutics. Chronobiology is the study of biological rhythms. These rhythms are explained by various terms as per the duration of the rhythmic cycle. The term 'circadian' explain thebiological rhythm cycle which finishes within a day i.e. within 24 hrs^[17]. Oscillations of shorter duration (more than one cycle for

each day) are named 'ultradian'. oscillation that are longer than 24 hrs are 'infradian' rhythms. Ultradian, circadian and infradian rhythms exist together at all degrees of biological organisation^[18].

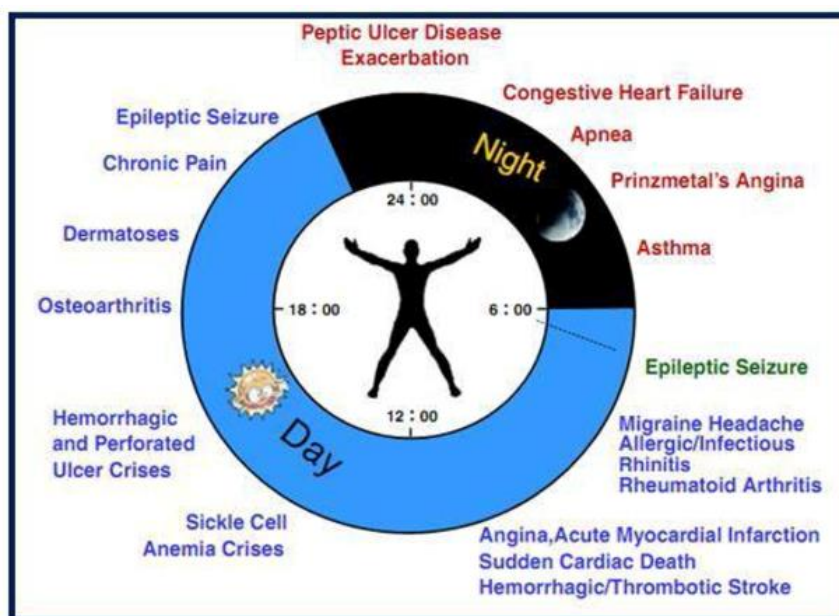


Pharmaceutics deals with the design and evaluation of pharmaceutical dosage forms or drug delivery systems to assure their safety, effectiveness, quality and reliability. The blend of every one of these characterized above has leads to the advancement of chronopharmaceutics, which manages improvement of pharmaceutical definitions that discharge the medication as per the biological rhythm of the disease.

Diseases with circadian rhythm to which cronopharmaceutics may entangle :

There are many diseases which can be entangled or be treated very effectively by using chronopharmaceutical drug delivery system (ChrDDS) over the conventional system^[19-22].

- (i) Bronchial asthma
- (ii) Prinzmetal's angina
- (iii) Arthritis
- (iv) Epilepsy
- (v) Sleep disorders
- (vi) Chronic Pain
- (vii) Anemia
- (viii) Cancer
- (ix) Cardiovascular diseases
- (x) Allergic rhinitis
- (xi) Diabetes
- (xii) Alzheimer's disease
- (xiii) Coagulation disorder and thrombosis
- (xiv) Hypercholesterolemia
- (xv) Parkinson's disease
- (xvi) Peptic ulcer



Chronopharmaceutical Drug Delivery Systems :

In 1980's, Lynch et al. revealed the most known parenteral Chronopharmaceutical DDS^[23]. A continuous drug delivery rates would be undeniably more valuable than a constant rate input. The most recent innovation to accomplish pulsatile or chronopharmaceutical medicate drug delivery includes utilizing microfabrication innovation^[24]. Perfect chronopharmaceutical DDS would assist with accomplishing once a day formulation with potential points of advantages and disadvantages.

Advantages	Disadvantages
reduced dosing frequency	delayed pharmacodynamic effect
enhanced patient compliance	increase hepatic metabolism
reduced toxicity, etc	reduced bioavailability
	sustained toxicity, etc.

As of now the most utilized chronopharmaceutical DDS are DIFFUCAPS^{®[25]}, CHRONOTOPIC^{TM[25]}, EGALET^{®[25]}, OROS^{®[26]}, CHOTIN^{®[27]}, CODAS^{TM[28]}, CEFORM^{TM[29]}, and GEOCLOCK^{TM[30]}.

Recent ChrDDS Available In Market^[23-34]:

For selection of appropriate technology we will have to take in consideration some factors such as the application range, ease of manufacture, cost-effectiveness and flexibility of the desired pharmacokinetic profile. Recognition of the importance of circadian rhythms, to physiology, pharmacology, molecular biology, and the health sciences has increased rapidly over the past few years.

Numerous innovations have been created for drug delivery to the body as per the biological rhythm of the diseases. The advancements in different system have been created taking chronopharmaceutics in thought. Systems like,

SR. NO.	SYSTEM	MECHANISM
1	GEOMATRIX®	The use of hydrophilic matrixes.
2	Hydrogels	Stimuli-sensitive – hydrogels and temperature sensitive hydrogels.
3	Controlled-release microchip	Microchip that can provide controlled release of single or multiple drug substances on demand.
4	CHRONOTOPIC®	Oluble or rupturable membrane system.
5	OROS®	Osmosis based system that delivers a bolus drug dose in a time- or site-specific manner.
6	CONTIN®	Complex formed between a cellulose polymer and a non-polar solid aliphatic alcohol (semi-permeable matrixes).
7	CODAS®	Contains mixture of both water-soluble and waterinsoluble polymers. It is a multiparticulate system designed for bedtime dosing.
8	DIFFUCAPS®	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.
9	TIMERx®	It is hypdrogel based controlled release device.
10	Physico-chemical modification of the API	This method is used to modify the physicochemical properties (e.g. solubility, partition coefficient, membrane permeability, etc.).
11	CEFORM®	Solid feedstock i.e. biodegradable polymer/ bioactive agents (combination of temperature, thermal gradients, mechanical forces and flow rate).
12	EGALET®	Impermeable shell with two lag plugs, After erosion of the inert plugs, the drug is released.
13	Infusion pumps	Implantable infusion pump containing drug. Drug delivery is by intraperitoneal route.
14	GeoClock®	The partial coating adjusts the core hydration process and minimizes the surface area available for drug release.
15	PORT®	It contains a polymeric core coated with a semi-permeable, rate-controlling polymer.

IMPORANCE OF CHRDDS

Why ChrDDS is important and have domination on other drug delivery system ?

Because,

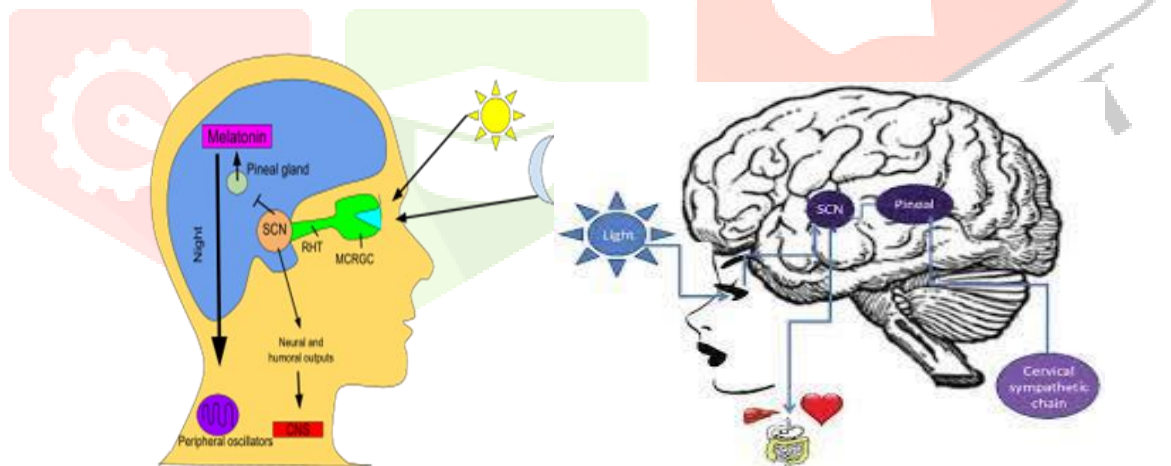
- Administration of two different simultaneously would be possible.
- It protects the drug to be deteriorated in the stomach.
- Risk of dose dumping can be avoided.
- Drug releases from the system after designing lag time according to the timing of disease.
- Lower dosing frequency.
- Fewer side effects.
- Better specificity in pharmaceutical activity.
- Better patient compliance.

APPLICATION OF CHRDDS

- To extend day time or night time activity.
- To reduce side effects.
- To reduce dosage frequency.
- To reduce dose size.
- To improve patient compliance.
- To lower the cost of therapy (as fewer dosage will require).
- For drugs to adapt circadian rhythm of body functions or diseases.
- For drug targeting to specific site.
- For Protection of mucosa from irritating drugs.
- For preventing drug loss from first pass metabolism.

CHRONBIOTICS

The term ‘chronobiotic’ was first used by Simpson et al.^[35] but it was not until much later that it became defined as a drug that specifically affects the physiological regulation of the biological time structure. Today, chronobiotic defines any chemical substance capable of therapeutically re-entraining desynchronized circadian rhythms or by increasing amplitude of rhythm, prophylactically preventing their disruption following environmental insult^[36,37]. The prototype of this type of drugs is melatonin. Melatonin is produced in most organisms, from algae to mammals, and its role varies considerably across the phylogenetic spectra^[38]. In humans, it plays a major function in the coordination of circadian rhythmicity, remarkable the sleep–wake cycle^[39,40].



Melatonin secretion is an ‘arm’ of the biological clock in the sense that it responds to signals from the suprachiasmatic nuclei (SCN) and in that the timing of the melatonin rhythm indicates the status of the clock, both in terms of phase and amplitude. From another point of view, melatonin is also a chemical code of night: the longer the night, the longer the duration of its secretion. In many species, this pattern of secretion serves as a time cue for seasonal rhythms^[41]. The greatest density of melatonin receptors in humans is located in the SCN^[42]. Entraining free-running circadian rhythms by administering melatonin is only possible if the SCN is intact. Daily timed administration of melatonin to rats shifts the phase of the circadian clock, and this phase shifting may partly explain melatonin effect on sleep in humans, or the ‘chronobiotic effect’. The evening increase in melatonin secretion is associated with an increase in the propensity for sleep^[43,44]. Secretion of melatonin during the day, as occurs in diverse pathological or occupational health situations, is strongly associated with daytime sleepiness or napping, and the administration of melatonin during the day induces sleepiness^[45]. The phase-shifting effects of melatonin were also sufficient to explain its effectiveness as a treatment for circadian-related sleep disorders such as jet lag or the delayed phase sleep syndrome

CONCLUSION:

A lot of progress has been accomplished towards chronopharmaceutical drug delivery system that can viably treat diseases with nonconstant dosing treatments, for example, seizures, asthma, cardiac problem, diabetes. A subsequent objective is to animate further experimental and clinical research in the field of chronopharmacology. Items that are right now being worked on for commercialization are for the conveyance of proteins, hormones.

Moreover, the body's biological time's structure must be counted and respected in the designing of pulsatile drug delivery system. By choosing ideal time to accomplish the desire effect, treatment options may emerge and undesired side effects can be limited. In any case, the most significant objective of the issue is to inspire the improvement and utilizations of chronotherapeutics as a commonsense method for improving the results and security of clinical treatment. In time where pharmaceutical organizations endeavor to offer better answers for the market the utilization of these clever solutions couldn't just offer better helpful outcomes yet in addition with the patient's compliances.

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