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A CURRENT UPDATE AND FUTURE PROSPECTS OF CHRONOMODULATED DRUG DELIVERY APPROACHES

Vimal raj. E[1], Ubaidulla Uthumansha[1*],

[1]Department of Pharmaceutics, Crescent school of Pharmacy, B.S. Abdur Rahman Crescent Institute of Science & Technology, GST Road, Vandalur, Chennai, Tamil Nadu, India. PIN-600048.
[1*]Associate Professor, Department of Pharmaceutics, Crescent school of Pharmacy, B.S. Abdur Rahman Crescent Institute of Science & Technology, GST Road, Vandalur, Chennai, Tamil Nadu, India. PIN-600048.

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Abstract

Chrono-modulated drug delivery systems have become a potentially useful approach for optimizing therapeutic outcomes by synchronizing drug administration with circadian rhythms and disease patterns. The circadian rhythm regulates various physiological processes, including drug absorption, distribution, metabolism, and elimination. Chrono-modulated drug delivery systems involve the controlled release of drugs at particular intervals to correspond with the body's natural rhythm. Two-thirds of asthma patients have nocturnal asthma, which is characterized by an increase in symptoms such as wheezing, tightness in the chest, increased reactivity of the airways, and deterioration of lung function during the night. Between midnight and 8:00 am, and particularly around 4:00 am, these symptoms manifest. Several strategies have been explored for designing chrono-modulated drug delivery systems, such as implantable devices, transdermal patches, and oral formulations with specialized release profiles. These systems incorporate various mechanisms, including pH-sensitive coatings, osmotic pumps, and programmable electronics, to achieve the desired temporal release pattern. The benefits of chrono-modulated drug delivery systems are extensive. By targeting drug administration during specific periods of disease activity or maximum need, therapeutic concentration levels can be optimized, leading to improved patient outcomes. Furthermore, by minimizing drug exposure during inactive disease phases, side effects and drug resistance can potentially be reduced. This review also highlights the challenges associated with developing chrono-modulated drug delivery systems, including formulation stability, release rate control, and regulatory approvals.

Keywords: chronotherapy, drug delivery, pulsatile drug delivery system.

INTRODUCTION

Controlled and targeted drug administration has supplanted traditional dose forms in recent years [1]. In order to target the precise spot, this system has focused on a continuous, variable, and sustained drug delivery method. Nevertheless, some medical disorders only manifest at particular times of the day or night, making it impossible for the traditional dosage form to release in a way that is appropriate [2]. These conditions need the medication to be released as a "pulse" following a predefined lag period; the drug must be produced so that the lag period is succeeded by a complete and quick medication release .

The term "chrono modulated drug delivery system" refers to this type of technology. It is also referred to as a pulsatile drug delivery system or a chrono regulated drug delivery system [3]. Recent update of types of chronomodulated drug delivery system is representing in **Figure 01**.Two-thirds of asthma patients have nocturnal asthma, which is characterized by an increase in signs like wheezing, tightness in the chest, increased reactivity of the respiratory system , and deterioration of respiratory system performance during the night. Between midnight and 8:00 am, and particularly around 4:00 am, these symptoms manifest [4]. Given that the patient is asleep, taking medication at midnight is inconvenient. For the best course of treatment, maintaining a steady medication level is not always necessary [5]. A medication should only be administered in the very minimum amount necessary. Based on the BCS categorization [6], it is classified as class 3. The intention was to have a six-hour delay, which that the medication as it would be released at 4:00 am after being taken at nightfall.

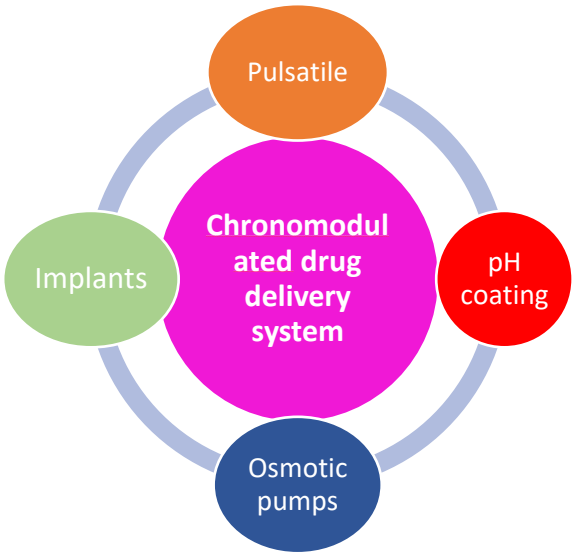

Figure:1. Formulation technique of chronomodulated drug delivery system

A chronic respiratory disease affecting millions of individuals worldwide is asthma. Asthma can currently be managed with a variety of therapeutic methods, such as injections, oral drugs, and inhalers [7]. On the other hand, patients' convenience and efficacy may be enhanced by the creation of a novel medication release mechanism tailored for asthma [8].

CHRONOTHERAPY

Chronotherapy is a treatment approach that focuses on the timing of medications or other interventions in order to optimize their effectiveness and minimize side effect [9]**.** It takes into account the natural rhythms and cycles of the body, including what time of day [10]. The circadian rhythm is an internal 24-hour clock that controls a number of physiological functions, including hormone synthesis, body temperature, metabolism and sleep-wake cycles [11]. By aligning the timing of treatments with the body's natural rhythm, chronotherapy aims to enhance therapeutic outcomes [12]. Among the various rhythms that have an impact on the human body are Ultradian: these are cycles that last less than a day, such as the 90-minute sleep cycle; Circadian: **Figure 2 and 3** displayed circadian sleep process and circadian activity. This includes patterns of sleep and wakefulness as well as infradian: cycles lasting more than 24 hours, such as monthly menstruation. [13]. Description of medical conditions and its medication based on circadian biology is shown in Table 1.

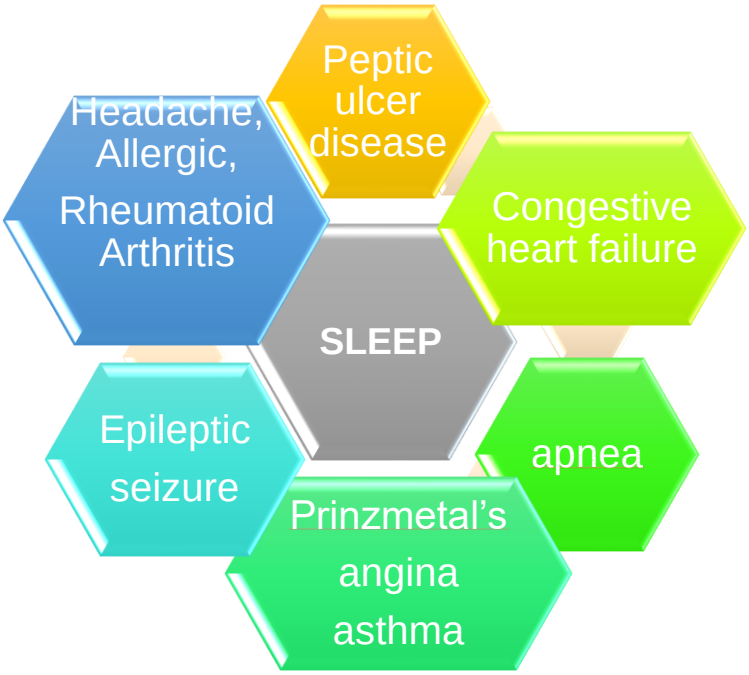

Figure:2 Diagram representative of circadian sleep

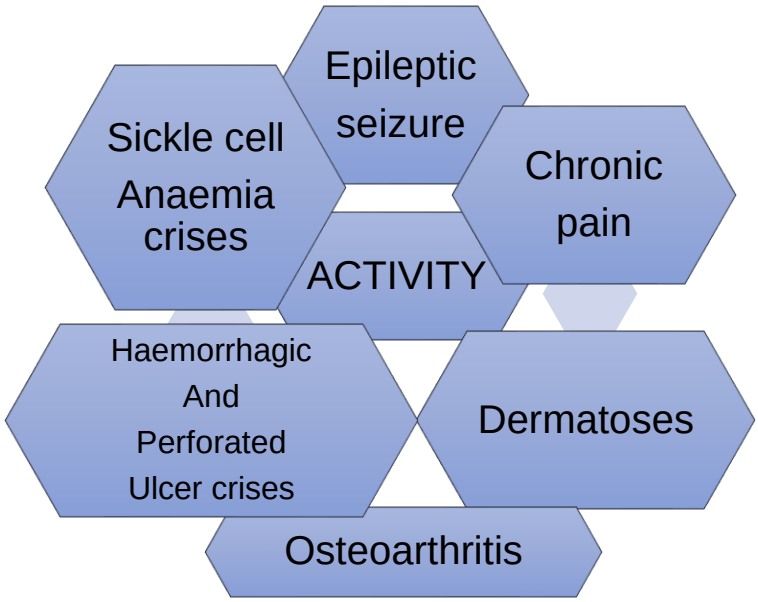

Figure:3 Diagram representative of circadian activity

Classification of Chronotherapeutic Drug Delivery:

Chronotherapeutic drug delivery is classified into three classes;

- ✓ Time controlled drug delivery Systems,

- ✓ Stimuli induced drug delivery and
- ✓ Externally regulated drug delivery [14].

Mechanism of drug release form enteric-coated pulsincap dosage form is representation with neat labled diagram (Figure 4). In (Figure 6) displayed Chronological behaviour and mechanism of chronomodulated drug delivery system delivered the drug molecules into systemic circulation.

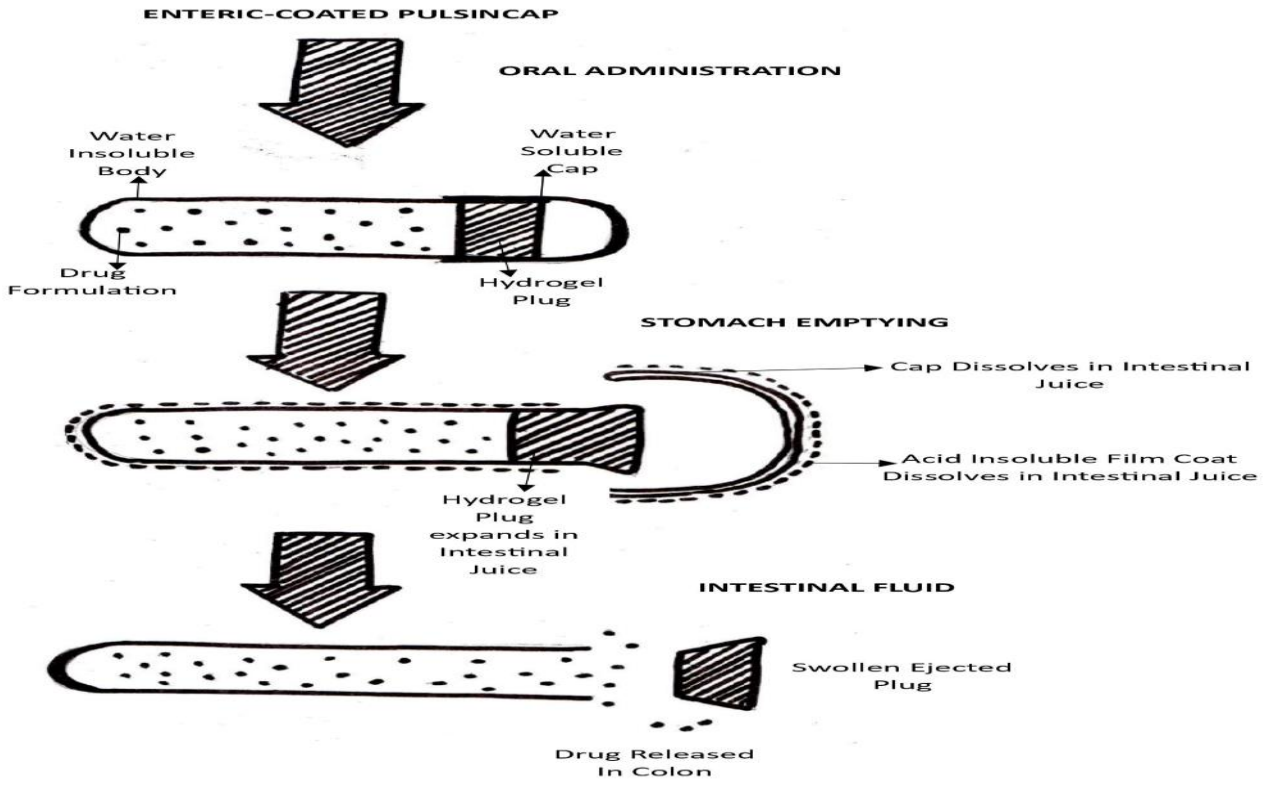

Figure: 4. Mechanism of drug release form enteric-coated pulsincap dosage form

ADVANTAGES OF CHRONOTHERAPY

- ➢ Drugs are not used in chronotherapy.
- ➢ A person receiving chromothy is more likely to benefit from numerous hours of sleep. Patients who receive chromothy frequently report feeling better and having more confidence.
- ➢ Because chronotherapy has a beginning, middle, and end, it differs from other forms of treatment. Thus, the point at which it will work may be predicted with ease.
- ➢ It provides you with a new routine, such as rising and sleeping earlier, which will be very strange for a few days but will give you time to mentally acclimate.

- Better stability and no chance of dose dumping Because chronotherapy has a beginning, middle, and end stage, prediction is simple [15].

DISADVANTAGES OF CHRONOTHERAPY

- When a patient sleeps during treatment or for longer than 24 hours after it ends, it is known as non-24-hour sleep wake syndrome.
- During chronotherapy, people become less productive, and staying up late until the other schedule is comfortable can be difficult.
- Having medical supervision is essential when using this therapy.
- Many process variables. The requirement for a professional and trained workforce in manufacturing [16].

CHRONOTHERAPY IN VARIOUS DISEASES

Chronotherapy of various diseases is shown in Table 01 and discussed in detail below.

Asthma:

Because of the inflammation of the airways associated with this illness, the lower respiratory tract becomes hyperresponsive to many environmental stimuli [17]. At night, the patient's airway resistance progressively worsens. Asthma is the most common ailment with a considerable time-related circadian fluctuation. Asthma episodes are most common in the early morning [18] and its biological mechanism is representing Figure 5. During the evening, asthma attacks are 50–100 times more prevalent. Asthma flare-ups during the night are a sign of a change in the biological functioning state brought on by alterations in hyperreactivity of the airways to acetylcholine, histamine, and house dust; and plasma cortisol, epinephrine, histamine, and cyclic AMP bronchial patency circadian rhythms. It has been demonstrated that once every day doses of the transdermal tulobuterol patch, sustained release theophylline, and glucocorticoid steroid cyclonite.

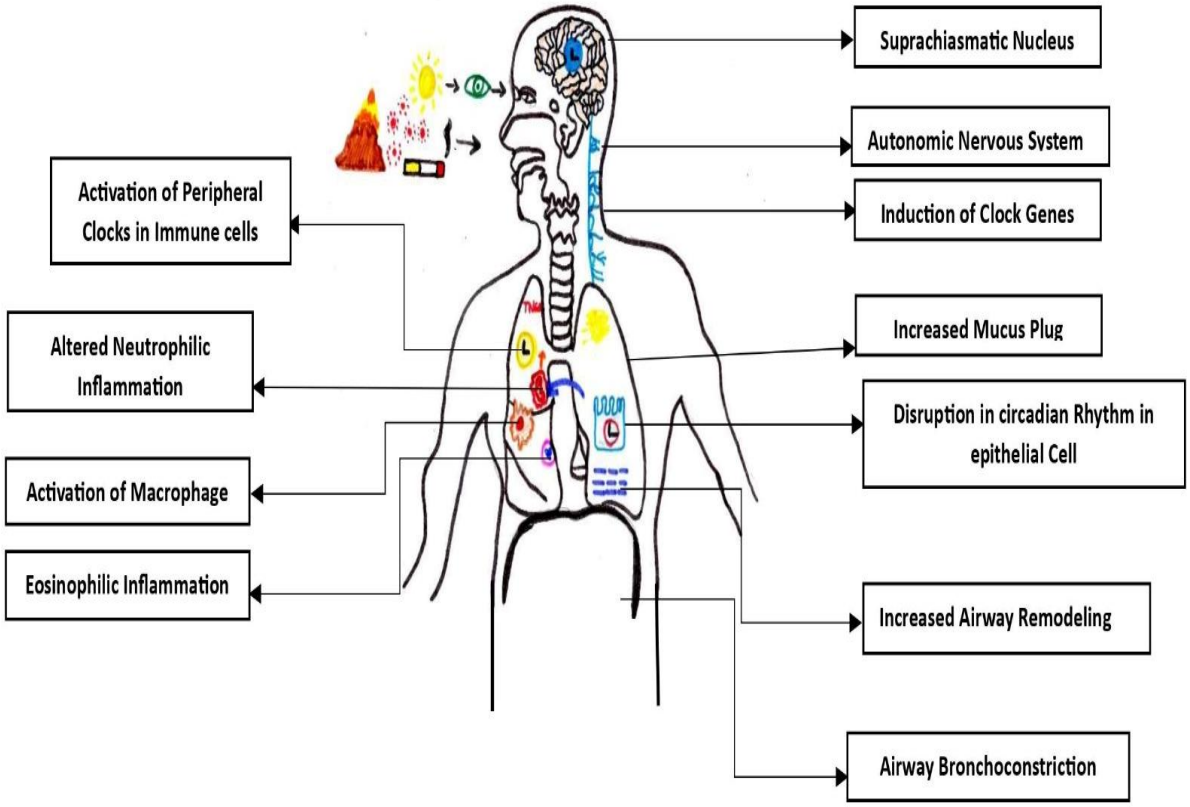

Figure 5. Biological mechanism of nocturnal asthma

Cardiovascular disease:

Mornings bring with them higher levels of capillary resistance and vascular reactivity. and lower in the afternoon under this state [20].Because of an increase in platelet aggregation and a decrease in fibrinolytic activity, the blood becomes relatively hypercoagulable in the morning [21]. Furthermore, blood pressure increases dramatically in the early morning hours after falling throughout the sleep cycle. Along with showing the unequal distribution of these events over a 24-hour period, these observations also show that the early afternoon and Higher predicted events of myocardial ischemia, angina pectoris, acute myocardial infarction, congestive cardiac failure, and sudden cardiac death occur in the early evening during the first few hours of the daily activity span [22]. Early in the morning is when sympathetic activity and the Renin-Angiotensin-Aldosterone axis peak.

Cancer:

Chemotherapy may be safer and more successful, according to research on both humans and animals, if cancer drugs are administered at precise timings that maximize tumor cell cycles while limiting toxicity to healthy tissue [24]. The cyclical

diurnal shifts both when the tumors are small and growing at their fastest rate and when they are larger and growing more slowly, in tumor blood flow and cancer growth are significant [25]. The frequency and quality of tumor response, maximum tolerated dose, average dose intensity, drug toxicity patterns and severity, and cancer patient survival rates are all significantly impacted by the timing of chemotherapy, which is based on circadian rhythms.

[26]. The pharmacologic and pharmacokinetic properties of the treatment, as well as regular fluctuations in mitotic activity, RNA translational activity, and DNA and RNA synthesis, may all have an impact on tumor cell susceptibility. It was found that the cancer chronogenetic therapy successfully inhibits tumor growth in living organisms [27]. For example, it has been demonstrated that the sensitivity to the anticancer medication cyclophosphamide is regulated by the Clock gene. [28].

Peptic ulcer:

The digestive system's many processes are regulated by rhythms of the circadian; for example, the production of gastric acid is greatest at night [29]. Small bowel movement, stomach emptying, and gastric acid production all slow down at night. A key element in the healing of duodenal ulcers is the suppression of nocturnal acid production.Therefore, the suggested dosage for H2 antagonists for an active duodenal ulcer is once daily at bedtime [30]. Chronotherapy, which blocks H2 receptors at night, can solve issues with a prolonged or significant drop in intragastric acidity for 24 hours, thereby reducing the risk of infection and infestation of the intestines, bacterial overgrowth, and the potential formation of N-nitrosamine [31].

Arthritis:

Osteoarthritis and rheumatoid arthritis can be distinguished from one another by observing when a patient's joints hurt the most during the day [32]. Rheumatoid arthritis is characterized by morning stiffness, while osteoarthritis usually worsens in the afternoon and evening. To ease the stiffness and morning discomfort associated with rheumatoid arthritis, non-steroidal anti-inflammatory medicines (NSAIDs) are better for the treatment when taken late at night [33]. When taken in the morning, the new cyclooxygenase-2 inhibitors effectively lessen the symptoms of osteoarthritis. When a small portion of the dosage is taken in the evening, better outcomes are observed in cases of rheumatoid arthritis. All types of arthritis are treated with chronotherapy, which entails the use of corticosteroids and non-steroidal anti-inflammatory medications [34].

Hypercholesterolemia:

Increased rates of cholesterol intake in relation to hepatic cholesterol and hypercholesterolemia generation occur in the evenings, even when fasting [35]. Free cholesterol levels have been found to peak in the morning and evening when HMG-CoA reductase antagonists are taken, and to be lowest between 2 and 6 pm [36].

Diabetes:

For those with diabetes type I, the circadian cycles of insulin and its effects are physiologically and therapeutically relevant [37]. Insulin is thus delivered pulsatilely, albeit irregularities may occur from time to time. Insulin has a cyclic rhythmicity of 8-30 minutes during which it can demonstrate optimal effect. The insulin release and action modulators' circadian pattern of secretion affects the insulin release mode. As a result, there is a There is a short-term rhythmicity difference between the maximum and minimum plasma insulin concentration, as well as a complex secondary circadian rhythm that varies between insulin resistance in the early morning and late afternoon. [38].

Sleep Disorders:

Numerous biological signals, including those related to sleep problems, are produced by the central and autonomous neural systems. These signals have a complicated temporal structure with pulsing and rhythmic fluctuations in multiple frequencies [39]. Circadian, rhythmic modifications to the biochemical, psychological, and physiological systems are the main causes of sleep. Disturbances in the circadian rhythm or abnormal physiological or psychological processes that transpire during sleep can give rise to a multitude of illnesses.Furthermore, individual differences in circadian rhythm disruptions exist, and determining each variation would be necessary for treating a particular sleep condition [40].

Alzheimer's Disease:

Individuals suffering from Alzheimer's disease also show changes in their circadian rhythm [41]. Individuals suffering from Alzheimer's disease show less macrophage activity during peak times, a higher percentage of nocturnal activity, and decreased inter-day stability in motor activity [42]. Patients with this illness have elevated core body temperatures, irregular circadian rhythms, and deteriorating cognitive and functional capacities [43].

Parkinson's Disease:

Numerous alterations to the circadian rhythm of blood pressure are brought on by the disease; postprandial hypotension and increased diurnal blood pressure variability are caused by autonomic dysfunction [44]. Nevertheless, because it is challenging to estimate the daily changes of the disease's phase-specific motor activity pattern and the consequent effect of drugs, the The clinical data for this disease have not evaluated the presence of a circadian rhythm. [45].

Chrono modulated drug delivery systems:

Chrono modulated drug delivery system used in various treatment for diseases like stomach ulcer [55], asthma [56], cardio vascular system [57], arthritis [58],diabetes mellitus[59] , hyper cholesterol[60].

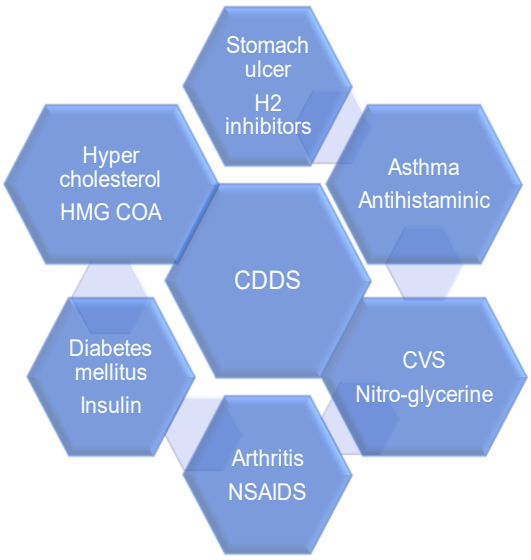

Figure :6 Chronological behaviour of chrono modulated drug delivery system

Table 1. Description of medical conditions and its medication based on circadian biology

S.No	Health Status	Body's Circadian Rhythms	Drugs Taken	Ref
1	Arthritis rheumatoid	Stiffness and joint discomfort in the morning	Glucocorticoids and nsaids	46
2	Inflammatory rhinorrhoea and bronchial asthma	Attacks that occur more frequently at night or in the early morning	Antihistaminic and b2 agonists	47
3	Heart-related conditions	During the sleep cycle, blood pressure is at its lowest and sharply increases when you get up in the morning.	Blockers of calcium channels and nitroglycerin	48
4	Diabetes type I	Elevation of blood sugar following a meal	Biguanide, insulin, and sulfonylurea	49
5	The syndrome of attention deficiency	An increase in afternoon levels of 3,4-dihydroxyphenylalanine	phenoperidine	50
6	Cancer	Rhythm-dependent variations in the toxicity of drugs	5. Leucovorin and fluorouracil	51
7	Headaches	Changes in Vasomotor Tone	Medications that prevent migraines	52
8	Convulsions	Early morning or nocturnal seizures	Antiepileptic medication	53
9	Gastrointestinal issues	Increased production of stomach acid at midnight	Antagonist of the h2 receptor	54

Conclusion

The body of research on In physiology, pharmacology, molecular biology, and the health sciences, circadian rhythms have grown significantly in the last several years. When it comes to drug delivery, traditional controlled-release formulations rely on one or more reservoirs or systems to maintain the drug concentration in vivo at the recommended dosage for an extended amount of time. While this is necessary, it is insufficient to treat disorders affecting the circadian rhythm.

Current conventional dose forms are ineffective in treating diseases with chronobiological pathogenesis. This issue is resolved by chemotherapeutic drug delivery systems (CDDS), which release drugs in accordance with the circadian rhythm and were developed using sigmoidal drug release. A chrono modulated system can be designed using a variety of strategies, such as a system that is triggered by stimuli, a system that is dependent on external stimuli, and a release system that is time-specific. This technique is beneficial for many diseases that follow circadian fluctuations, such as diabetes, hypertension, asthma, and cardiovascular disease.

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