# Chrono-modulated drug delivery system approaches, evaluations and in vitro in vivo evaluations

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***Abstract:***

*Chrono-modulated drug delivery systems represent a promising frontier in the field of pharmacology, capitalizing on the intricate interplay between drug administration timing and the body's circadian rhythms. This review explores the latest developments in Chrono-pharmacology, emphasizing the design and application of drug delivery systems tailored to the body's natural biological clock. The article delves into the molecular and physiological foundations of circadian rhythms, the impact of timing on drug pharmacokinetics and pharmacodynamics, and the clinical implications of adopting Chrono-modulated approaches in various therapeutic areas. Technological developments that allow for scheduled medication release mechanisms—like nanotechnology and programmable pumps—are explored in conjunction with their use to chronotherapy. Successful CMDDS uses in oncology, cardiovascular illnesses, and sleep problems are demonstrated by case studies. Future research paths in personalized medicine, regulatory considerations, and patient variability in circadian rhythms are among the challenges that are discussed. Enhancing patient care and treatment outcomes may be achieved by comprehending and utilizing circadian rhythms in medication distribution.*

***Key Words:*** *Chrono-modulated, circadian rhythms, body's natural biological clock, drug delivery, cardiovascular illnesses.*

## 1. Introduction:

The intricate dance between circadian rhythms and drug pharmacokinetics has spurred a transformative wave in pharmaceutical research, giving rise to the burgeoning field of Chrono-modulated drug delivery systems. The circadian system, governed by a network of molecular clocks orchestrating a 24-hour rhythm, extends its influence beyond sleep-wake cycles to intricately modulate physiological processes, including drug metabolism and response [1]. This dynamic relationship has prompted a paradigm shift in drug administration

strategies, with a growing emphasis on synchronizing therapeutic interventions with the body's natural circadian rhythm.

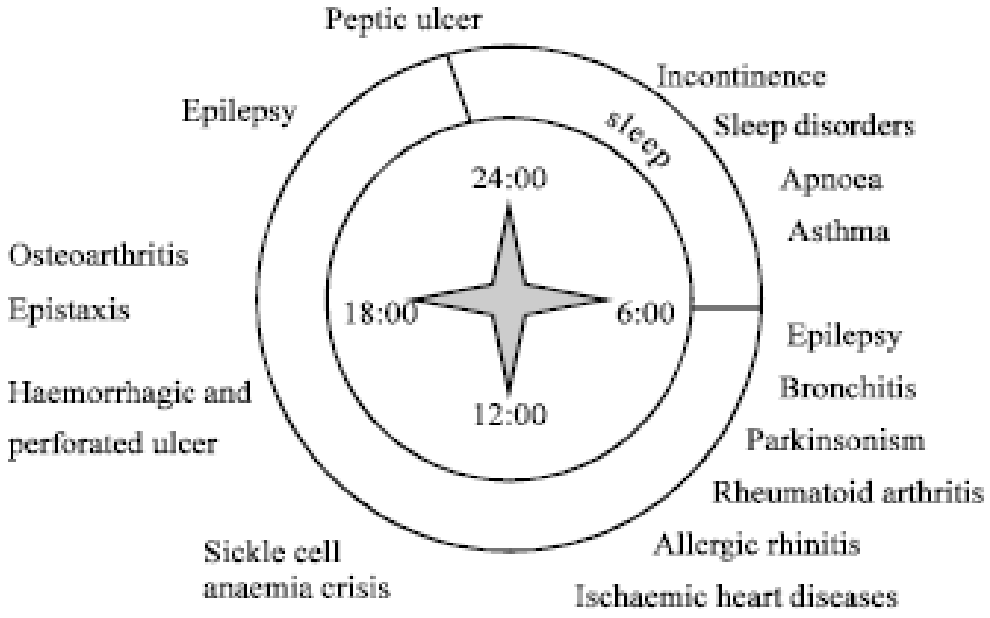



**Figure1: Display in the form of a 24 h clock diagram of the approximate time, in human following the diurnal activity/nocturnal sleep routine, when symptoms or events of diseases are worst or most frequently.**

Circadian influences on drug absorption, distribution, metabolism, and elimination are multifaceted and well-documented across various drug classes and therapeutic areas [2]. As researchers unravel the molecular intricacies of circadian rhythms, the potential to harness these temporal patterns for optimized drug delivery becomes increasingly apparent. Chrono-modulated drug delivery systems, designed to release therapeutic agents at specific times to align with circadian peaks of efficacy and receptivity, represent a novel approach to enhancing treatment outcomes while minimizing adverse effects.

This review aims to provide a comprehensive exploration of Chrono-modulated drug delivery systems, delving into the mechanisms that underlie their functionality, the benefits they offer in disease management, and the challenges associated with their implementation. By understanding the circadian variations in diseases across diverse medical domains, researchers and clinicians can tailor drug delivery strategies to exploit optimal windows of efficacy. Such an approach holds the potential to revolutionize the landscape of pharmacotherapy and usher in a new era of personalized and precise treatment regimens.

The recognition of circadian influences in drug response is not confined to a single therapeutic area. In oncology, for instance, the synchronization of chemotherapy with the circadian rhythm of tumor growth has shown promise in improving treatment efficacy and minimizing toxicity [3]. Similarly, cardiovascular diseases, marked by diurnal variations in blood pressure and heart rate, present an opportunity for Chrono-modulated interventions [4]. These examples underscore the potential breadth of impact that Chrono-modulated drug delivery systems could have on diverse medical fields. As we delve into the complex interplay between circadian rhythms and pharmacokinetics, it becomes evident that the temporal dimension of drug administration is a critical factor in achieving therapeutic precision. By exploring the mechanisms, benefits, and challenges associated with Chrono-modulated drug delivery, this review aims to contribute to the growing body of knowledge that underpins the future of circadian-aligned pharmacotherapy.

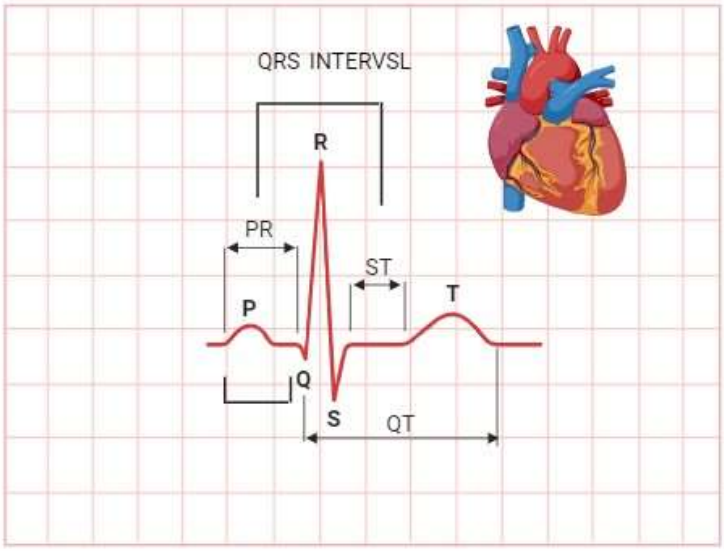



**Figure 2: electrocardiogram (ECG)**

## 2. OVERVIEW OF DISEASE:

Circadian rhythms intricately weave their influence through the fabric of numerous diseases, manifesting temporal variations in symptom severity, disease progression, and treatment responsiveness. The recognition of these circadian patterns extends across diverse medical domains, underscoring the importance of understanding the temporal dynamics inherent in various pathological processes.

In oncology, tumors exhibit circadian rhythmicity in their growth rates and responsiveness to treatment [5]. The molecular clock's impact on cell cycle regulation and DNA repair mechanisms contributes to the observed variations in the efficacy of chemotherapeutic interventions at different times of the day [6]. This inherent temporal dimension prompts a reevaluation of treatment protocols, with Chrono-

modulated drug delivery systems offering a potential avenue for optimizing therapeutic outcomes in cancer patients.

Cardiovascular diseases, marked by diurnal variations in blood pressure and heart rate, present another realm where circadian rhythms play a pivotal role [7]. The propensity for adverse cardiovascular events shows a time-of-day dependence, suggesting that interventions tailored to the circadian patterns of the cardiovascular system could be advantageous [8]. By aligning drug administration with the physiological peaks and troughs, Chrono-modulated drug delivery systems hold promise in mitigating the circadian-associated risks in cardiovascular medicine.

Neurological disorders, metabolic syndromes, and endocrine dysregulations also exhibit temporal variations in their clinical manifestations. For instance, conditions such as epilepsy may display circadian rhythmicity in seizure occurrence, influencing the timing of antiepileptic drug administration [9]. Similarly, disorders characterized by disruptions in hormonal secretion, such as diabetes, may benefit from Chrono-modulated approaches to optimize the therapeutic impact of medications [10].

Understanding these disease-specific circadian variations is paramount for tailoring drug delivery strategies that exploit the optimal windows of efficacy. The ability to synchronize therapeutic interventions with the circadian rhythms inherent in various diseases holds the potential to revolutionize treatment paradigms, enhancing both efficacy and patient outcomes.

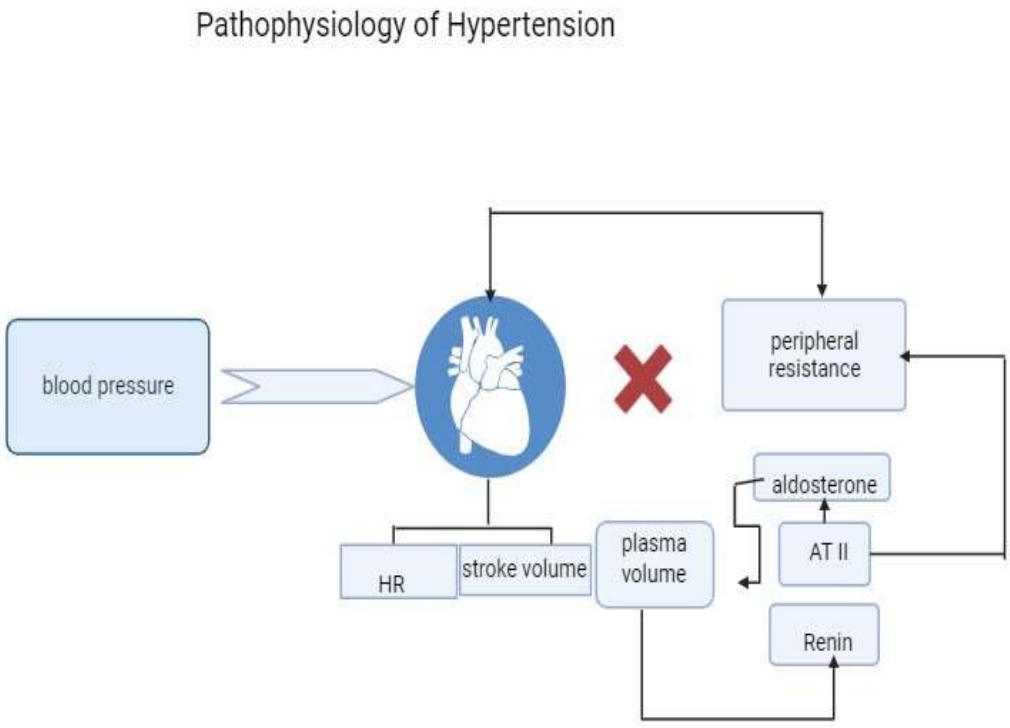



**Figure 3: pathophysiology of hypertension**

## 3. CHRONOMODULATED DRUG DELIVERY SEYTEM AND THEIR MACHANISM:

Chrono-modulated drug delivery systems represent a groundbreaking approach designed to synchronize drug release with the body's circadian rhythms, optimizing therapeutic outcomes. These systems leverage the temporal variations in drug absorption, distribution, metabolism, and elimination to achieve targeted and controlled delivery during specific periods of heightened efficacy or reduced side effects.

- **FORMUALTION STRATEGIES**: One key mechanism involves the use of innovative formulation strategies to control drug release. Time-controlled pulsatile systems and osmotic pumps are examples of technologies allowing for gradual drug release at predetermined times [11]. These strategies aim to mimic the natural circadian fluctuations in drug metabolism, ensuring that the therapeutic agent is delivered when its effects are maximized.

- **TARGETED DELIVERY SYSTEM**: Another mechanism centers on targeted drug delivery systems, utilizing nanotechnology to enhance precision. Liposomes and nanoparticles are engineered to encapsulate drugs, facilitating their delivery to specific tissues or organs during their most receptive phases [12]. This targeted approach minimizes off-target effects and maximizes therapeutic impact. These mechanisms collectively contribute to the overarching goal of Chrono modulated drug delivery systems — achieving a harmonious alignment between drug administration and the body's circadian rhythms. This temporal synchronization has the potential to enhance treatment efficacy, minimize adverse effects, and improve patient compliance.

### 3.1 BENEFITS OF CHRONOMODULATED DRUG DELIVERY IN DISEASE:

Chrono-modulated drug delivery systems offer a range of advantages in disease management, providing a targeted and time-sensitive approach to therapeutic interventions.

**[1] ENHENCED EFFICACY:** Aligning drug administration with circadian rhythms can enhance treatment efficacy. In oncology, for instance, studies have demonstrated improved antitumor effects when chemotherapeutic agents are administered at specific times, capitalizing on circadian variations in tumor sensitivity [13].

**[2] REDUCED SIDE EFFECTS:** By releasing drugs during periods of heightened receptivity, Chrono-modulated drug delivery systems have the potential to minimize side effects. This temporal optimization aims to exploit periods when the body is

more tolerant to the therapeutic agent, as observed in cardiovascular medicine, where blood pressure and heart rate exhibit diurnal variations [14].

**[3] IMOROVED PATIENT COMPLIANCE:** The timed release of drugs can be tailored to align with patients' daily routines, potentially improving adherence treatment regimens. This can lead to better disease management outcomes, particularly in chronic conditions where long-term adherence is crucial [15].

**[4] PERSONALIZED TREATMENT:** Chrono-modulated drug delivery allows for a more personalized treatment approach, considering individual variations in circadian rhythms. Tailoring drug administration to patients' unique circadian profiles may optimize therapeutic outcomes and minimize adverse reactions [16].

**[5] OPTIMIZED CHRONO- PHARMACOKINETICS:** Understanding and utilizing Chrono-pharmacokinetics can lead to optimal drug exposure. Circadian variations in drug absorption, distribution, metabolism, and elimination can be harnessed to achieve better drug bioavailability and pharmacological response [17].

### 3.2 CHALLENGES IN IMPLEMENTING CHRONOMODULATED DRUG DELIVERY SYSTEM:

Despite the potential benefits, the implementation of Chrono-modulated drug delivery systems faces several challenges that span biological complexities, technical hurdles, and practical considerations.

#### [1] BIOLOGICAL CHALLENGES:

- Inter-individual variability: circadian rhythms vary widely among individuals, making it challenging to establish universal drug administration schedules [18].
- Diseases-specific variations: diseases may exhibit unique circadian patterns, requiring tailored approaches. Adapting to the circadian dynamics of specific conditions poses a challenge in universal system design [19].

#### [2] TECHNICAL AND FORMULATION CHALLENGES:

- Precision in formulation: designing formulations that precisely adhere to circadian rhythms is a complex task. Achieving the desired temporal release profiles poses challenges in formulation design.

- Manufacturing complexity: implementing and scaling up the production of Chrono-modulated drug delivery systems may present manufacturing challenges, impacting their widespread availability [20].

#### [3] PRACTICAL CHALLENGES:

- Patient compliance: Timed drug administration may be impractical for certain patient populations, affecting overall compliance. Ensuring that patients adhere to precise dosing schedules represents a significant challenge [21].

- Clinical adoption: integrating Chrono-modulated drug delivery into routine clinical practice requires overcoming institutional and logistical barriers. Clinical adoption may be hindered by the need for specialized infrastructure and training [22].

**[4] NEED FOR PERSONALIZATION:**

Patient specific chronotherapy: tailoring chronotherapy to individual patient circadian rhythms necessitates personalized approaches. Implementing such strategies on a large scale may be logistically challenging [23].

### 3.3 NEED FOR CHRONOMODULATED DRUG DELIVERY SYSTEM?

The development and implementation of Chrono-modulated drug delivery systems arise from a compelling need to address inherent limitations in conventional drug administration. This approach is driven by a recognition of the crucial role that circadian rhythms play in influencing disease dynamics and therapeutic responses.

**[1] CIRCADIAN VARIATIONS IN DISEASES:**

Diseases often exhibit circadian variations in their manifestations, influencing factors such as symptom severity and treatment responsiveness [24]. For instance, in cardiovascular diseases, the risk of adverse events follows a circadian pattern, emphasizing the importance of aligning interventions with the body's temporal dynamics [25].

**[2] OPTIMIZING THERAPUTIC EFFICACY:**

The need for Chrono-modulated drug delivery stems from the potential to enhance therapeutic efficacy. By synchronizing drug administration with the periods of heightened receptivity, this approach aims to maximize the impact of therapeutic agents when they are most effective [26]. This is particularly evident in the field of oncology, where circadian-timed chemotherapy has shown improved treatment outcomes [27].

**[3] MINIMIZING SIDE EFFECTS:**

Circadian-aligned drug delivery systems offer the prospect of reducing side effects by releasing drugs during periods when the body is more tolerant or less susceptible to adverse reactions [28]. This is crucial for improving patient tolerability and adherence to treatment regimens.

**[4] INDIVIDUALIZED TREATMENT:**

The need for personalized medicine is underscored by the recognition of individual variations in circadian rhythms. Chrono modulated drug delivery systems present an opportunity to tailor treatment regimens based on the unique circadian profiles of patients, optimizing therapeutic outcomes [29].

**[5] MITIATING BIOLOGICAL VARIABILITY:**

The biological variability in circadian rhythms among individuals poses challenges in achieving consistent treatment outcomes. Chrono modulated drug delivery addresses this variability by providing a dynamic and adaptable approach to drug administration [30].

In conclusion, the need for Chrono modulated drug delivery systems arises from a profound understanding of the temporal intricacies inherent in diseases and therapeutic responses. By harnessing the power of circadian rhythms, this approach seeks to revolutionize drug administration strategies, offering the potential for more effective, personalized, and tolerable treatments.

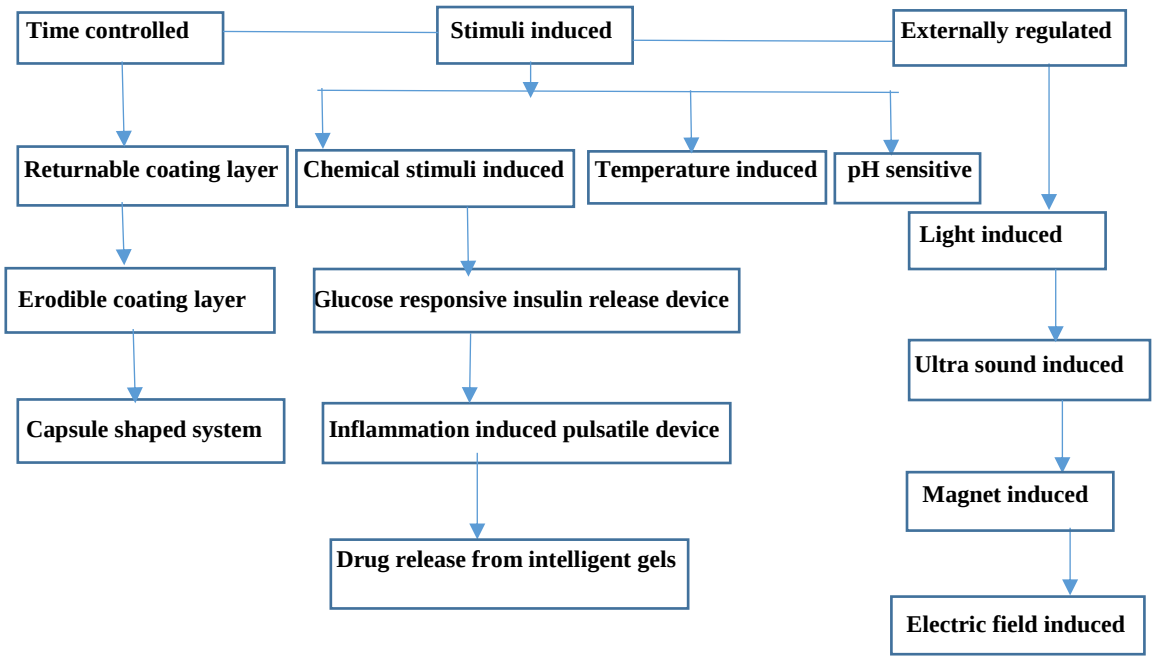
### 3.4 APPROACHES OF CHRONOMODULATED DRUG DELIEVRY SYSTEM

**1.** Time controlled drug delivery system

**2.** Stimuli induced Chrono-modulated drug delivery system

**3**. Externally regulated pulsatile drug delivery system

### 4. CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEM




### 4.1 TIME CONTROLLED PULSATILE DRUG DELIVERY SYSTM

Time-controlled pulsatile drug delivery systems, following a predefined lag time, release medications in a transient and rapid way within a defined time frame. These

systems offer better therapeutic efficacy and enhanced patient compliance since they can be adjusted independently of environmental influences.

### 4.2 STIMULI INDUCED PULSATILE DRUG DELIVERY SYSTEM

Stimuli- induced pulsatile drug delivery system are designed to release drugs in response to specific physiological or environmental triggers. These system aim to deliver the drug at the right time, lag site and in the right amount, which can be more beneficial than conventional dosages forms.

### 4.3 EXTERNALLY REGULATED PULSATILE DRUG DELIEVRY SYSTEM

Externally regulate time controlled pulsatile release system in time controlled drug delivery pulsatile release is obtained after a specific time interval in order to mimic the circadian rhythm. Such type of pulsatile drug delivery system contains two components: one is of immediate release type and one is a pulsatile release type.

## 5. ADVANTAGES OF CHRONOMODULATED DRUG DELIVERY SYSTEM:

The implementation of Chrono modulated drug delivery systems offers several advantages, providing a targeted and time-sensitive approach to drug administration.

### [1] ENHANCED THERAPUTIC EFFICACY:

Chrono modulated drug delivery systems aim to release therapeutic agents during periods of heightened receptivity, aligning with circadian rhythms. This approach has demonstrated potential for maximizing drug efficacy, particularly in diseases with circadian variations, such as cancer [31].

### [2] MINIMIZE SIDE EFFECTS:

By releasing drugs during periods when the body is less susceptible to adverse reactions, Chrono modulated drug delivery systems have the potential to reduce side effects? This can lead to improved tolerability and patient compliance [32].

### [3] IMPROVE PATIENT COMPLIANCE:

Tailoring drug administration to align with patients' daily routines can enhance compliance. The timed release of drugs minimizes the need for frequent dosing, making it more convenient for patients to adhere to prescribed regimens [33].

### [4] PERSONALIZED MEDICATION:

Chrono modulated drug delivery allows for personalized treatment regimens, considering individual variations in circadian rhythms. This personalized approach may optimize therapeutic outcomes by tailoring drug administration to each patient's unique biological clock [34].

**[5] COST EFFECTIVENESS:**

Optimizing drug release based on circadian rhythms may lead to more efficient use of therapeutic agents. This targeted approach can potentially reduce the overall amount of drug required for effective treatment, offering cost-effective benefits [35].

**[6] OPTIMIZED CHRONO-PHARMACOKINETICS:**

Understanding and utilizing Chrono-pharmacokinetics can result in optimal drug exposure. By aligning drug administration with the body's natural rhythms, Chrono modulated drug delivery systems can achieve better bioavailability and pharmacological response [36].

**5.1 DISADVANTAGES OF CHRONOMODULATED DRUG DELIVERY SYSTEM:**

While Chrono modulated drug delivery systems offer promising advantages, their implementation is not without challenges and drawbacks. Understanding the limitations is crucial for a comprehensive assessment of this innovative approach.

**[1] BIOLOGICAL VARIABILITY:**

The inherent inter-individual variability in circadian rhythms poses a significant challenge to the universal application of Chrono modulated drug delivery. Individual differences in the timing and magnitude of circadian peaks and troughs may impact the effectiveness of timed drug administration [37].

**[2] COMPLEX FORMULATION:**

Designing formulations that precisely adhere to circadian rhythms is a complex task. Achieving the desired temporal release profiles requires sophisticated formulation strategies, and the development of such formulations can be technically challenging [38].

**[3] MANUFACTURING COMPLEXITY:**

Implementing and scaling up the production of Chrono modulated drug delivery systems may present manufacturing challenges. The complexity of the formulations and the need for precision in timed drug release add intricacies to the manufacturing process [39].

**[4] PATIENT COMPLIANCE:**

Timed drug administration may pose practical challenges for certain patient populations. Patients may find it difficult to adhere to precise dosing schedules, potentially impacting the effectiveness of the treatment [40].

**[5] CLINICAL ADOPTION:**

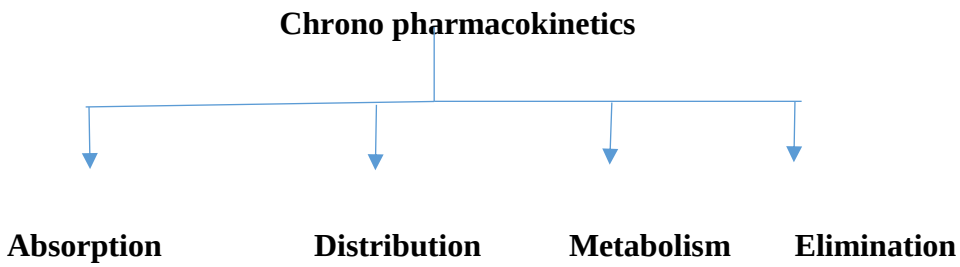
Integrating Chrono modulated drug delivery into routine clinical practice faces hurdles related to institutional and logistical barriers. The need for specialized infrastructure, training, and a shift in clinical protocols may slow down widespread adoption [41].

**[6] INDIVIDULIZED CHRONOTHERAPY:**

Tailoring chronotherapy to individual patient circadian rhythms may be logistically challenging on a larger scale. The need for personalized treatment plans based on individual circadian profiles introduces complexities in treatment standardization [42].

**6. CHRONO- PHARMACOKINETCS:**

Chrono pharmacokinetics explores the temporal variations in drug absorption, distribution, metabolism, and elimination, emphasizing the influence of circadian rhythms on the pharmacokinetic profile of drugs.




**[1] ABSORPTION :**

Circadian rhythms impact gastrointestinal function, affecting the absorption of drugs. For example, studies have shown that the absorption of certain drugs, like levofloxacin, varies throughout the day, with higher bioavailability observed in the evening [43].

**[2] DISTRIBUTION:**

The circadian rhythm can influence factors such as blood flow and body temperature, affecting drug distribution. These variations may impact the volume of distribution and tissue-specific concentrations of drugs [44].

**[3] METABOLISM:**

Enzymes involved in drug metabolism, such as cytochrome P450 enzymes, exhibit circadian variations. The activity of these enzymes can impact the rate at which drugs are metabolized, influencing their therapeutic efficacy and potential for side effects [45].

### [4] ELIMINTION:

Renal function, responsible for the elimination of many drugs, follows a circadian pattern. Variations in glomerular filtration rate and renal blood flow can affect the clearance of drugs, leading to fluctuations in their plasma concentrations [46].

Understanding the Chrono pharmacokinetics of drugs is crucial for optimizing therapeutic outcomes. Tailoring drug administration to align with circadian rhythms can enhance drug efficacy, reduce side effects, and contribute to personalized treatment strategies.

## 7. PHARMACODYNAMICS OF CHRONOMODULATED DRUG DELIVERY:

### [1] TARGETD THERAPUTIC ACTION:

Chrono modulated drug delivery aims to synchronize drug release with the body's circadian rhythms, optimizing the therapeutic action during specific periods. This can enhance the drug's effectiveness by aligning peak concentrations with the times of maximal disease activity or receptivity [47].

### [2] REDUCED SIDE EFFECTS:

By releasing drugs during periods of reduced susceptibility to adverse reactions, Chrono modulated drug delivery has the potential to minimize side effects. This is particularly relevant in conditions where circadian variations influence drug metabolism and toxicity [48].

### [3] CIRCADIAN-DRIVEN RECEPTOR SENSITIVITY:

The efficacy of certain drugs is influenced by the circadian variations in receptor sensitivity. Chrono modulated drug delivery systems can exploit these variations to achieve optimal receptor mengagement, potentially enhancing therapeutic outcomes [49].

### [4] CHRONO-PHARMACOKINETIC INTERPLAY:

The pharmacodynamics of Chrono modulated drug delivery are intricately linked to Chrono-pharmacokinetics. The temporal release of drugs influences their concentration-time profiles, which, in turn, dictates the pharmacodynamics response. This interplay is crucial for achieving the desired therapeutic effect [50].

While these general concepts provide an understanding of the pharmacodynamics of Chrono modulated drug delivery, the specific details would vary based on the drug's mechanism of action, the disease being treated, and the targeted therapeutic goals.

## 8. STRATEGIES OF CHRONOMODULATED DRUG DELIVERY SYSTEM:

Chrono modulated drug delivery systems employ various strategies to synchronize drug release with the body's circadian rhythms, optimizing therapeutic outcomes. These strategies encompass innovative approaches in drug formulation and delivery,

providing targeted and time-sensitive administration. Below are key strategies with relevant citations:

**[1] TIME CONTROLLED PULSATILTE SYSTEM:**

This strategy involves the design of drug delivery systems that release medications in a pulsatile manner at specific times of the day. Mimicking natural circadian fluctuations, these systems aim to align drug release with periods of increased efficacy. [51]

**[2] OSMOTIC PUMPS:**

Osmotic pumps are devices designed to deliver drugs at a controlled rate over an extended period. By adjusting the pump's characteristics, drug release can be timed to coincide with circadian rhythms, optimizing delivery during periods of heightened therapeutic effect. [52]

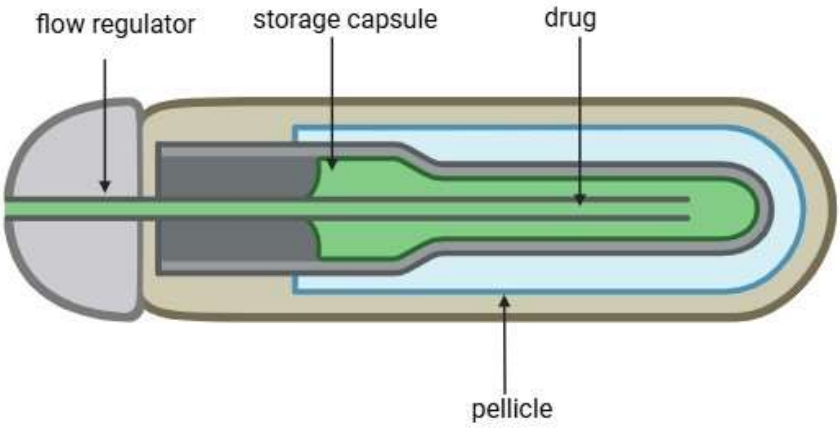



**Figure 4: osmotic pump**

**[3] TARGETD DELIVERY SYSTEM:**

Nanoparticle-based systems, including liposomes and nanoparticles, enable targeted drug delivery to specific tissues or organs. These systems can be engineered to release drugs when the target site is most receptive, minimizing off-target effects. [53]

**[4] pH-RESPONSIVE SYSTEM:**

PH-responsive drug delivery systems take advantage of pH variations in different body compartments. By responding to circadian-driven changes in pH, these systems allow for timed drug release, optimizing absorption and therapeutic effects. [54]

**[5] BIOLOGICAL CLOCK-RESPONSIVE SYSTEM:**

Innovative approaches involve drug delivery systems that respond to the body's biological clock, such as specific biomarkers or signaling pathways influenced by circadian rhythms. This dynamic response allows adaptive drug release. [55]

**[6] SMART HYDRIGELS:**

Smart hydrogels respond to environmental stimuli, such as changes in temperature or ph. These can be engineered to release drugs in response to circadian variations, providing a controlled and timed drug delivery mechanism. [56]

**9. DIFFERENT DOSAGES FORMS USED IN CHRONOMODULATED DRUG DELIVERY SYSTEMS:**

**[1] CHRONOMODULATED TABLETS:**

**Figure 5: Chrono-modulated tablets**

Tablets are a common dosage form for Chrono modulated drug delivery. These tablets are designed to release the drug at specific times to coincide with the body's circadian rhythms. [57]

**[2] CHRONOMODULATED CAPSULES:**

Capsules can also be formulated to achieve Chrono modulation. The release profile is tailored to match the therapeutic requirements during specific periods of the day. [58]

**Figure 6: Chronomodulated capsules**

**[3] CHRONOMODULATED NANOPARTICLES:**

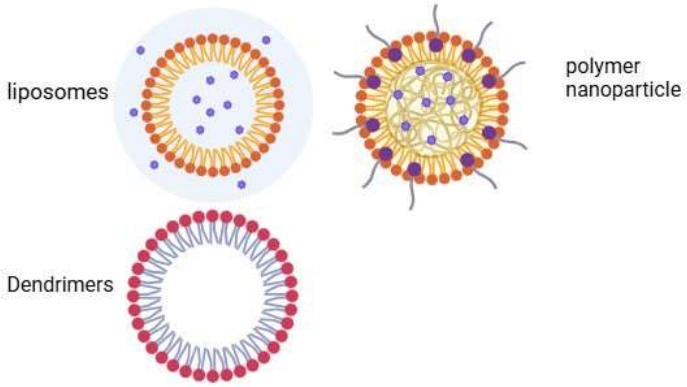



**Figure 7: Chrono-modulated nanoparticles**

Nanoparticles offer a promising avenue for Chrono modulated drug delivery due to their size and surface characteristics. They can be engineered to release the drug in a time-dependent manner. [59]

**[4] TRANSDERMAL CHRONOMODULATED PATCHES:**

**Figure 8: transdermal Chrono-modulated patches**

Patches provide a non-invasive approach to Chrono modulated drug delivery. They are designed to adhere to the skin, releasing the drug gradually over a specified period. [60]

**[5] INTRAVENOUS CHRONOMODULATED INFUSIONS:**

Intravenous infusions can be adapted to follow circadian rhythms, ensuring a timed release of the drug directly into the bloodstream. [61]

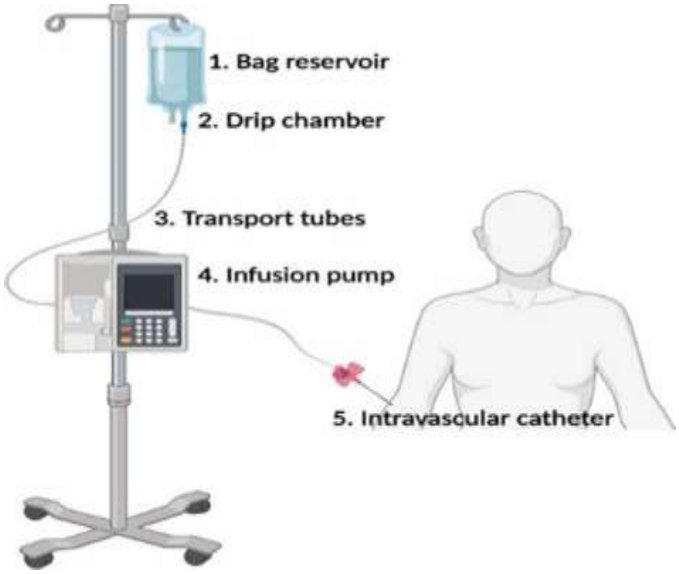



**Figure 9**: **Intravenous Chrono modulated Infusions in human**

| S.no | Drugs name | Disease name |
|---|---|---|
| 1. | Amlodipine | Hypertension [62] |
| 2. | Doxorubicin liposomes | Cancer[63] |
| 3. | Prednisone | Rheumatoid arthritis[64] |
| 4. | levodopa | Parkinson's disease[65] |
| 5. | Tacrolimus chronotheraputic | Immune related disorders[66] |

| | | |
|---|---|---|
| | formulation | |
| 6. | theophylline | Nocturnal asthma[67] |
| 7. | Salbutamol sulphate | Nocturnal asthma[68] |
| 8. | Verapamil(calan) | Hypertension, angina [69] |
| 9. | Trandolapril (Mavil) | Congestive heart failure[70] |
| 10. | Prednisone | Rheumatoid arthritis, asthma [71] |
| 11. | Leuprolide(Lupron) | Prostate cancer[72] |
| 12 | Ritalin | Attention deficit hyperactivity disorder[73] |
| 13. | Lutrepulse(leuprolide) | Hormone therapy for infertility [74] |
| 14. | Nicotine | Smoking cessation[75] |
| 15. | Irbesartan | Hypertension [76] |
| 16. | Nifedipine | Angina pectoris [77] |
| 17. | Montulokast sodium | Nocturnal Asthma [78] |
| 18. | Naproxen | Rheumatoid arthritis[79] |
| 19. | captopril | Hypertension, heart failure[80] |

**Table 1: name of drugs and diseases which can be used as the Chrono modulated drug delivery system**

## 10. EVALUTIONS OF CHRONOMODULATED DRUG DELIEVRY SYSTEM

### 10.1 HARDNESS

An assessment of the prepared tablets' hardness was conducted. It was conducted using Monsanto and the hardness was stated in kg/cm.


**Figure: 10 Monsanto hardness tester**

### 10.2 FRIABILITY TEST

The friability was determined using the friability test apparatus 20 tablets from each batch were weighed separately (W initial) and placed in the friabilator, which was then operated for 100 revolutions at 25 rpm [21]. The tablets were reweighed (W final) and the percentage friability was calculated for each batch by using the formula

**Friability = [(W1−W 2)/W1]*100.**

Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing.

### 10.3 WEIGHT VARIATION TEST

Weighing each of the twenty tablets that were randomly chosen from the lot, the average weight was calculated. The percentage of weight variation between each tablet and the average weight was thoughtful. The test criteria are satisfied if at least two of the each weight differs by more than 5% from the average weight.

### 10.4 DRUG CONTENT

The amount of medication in the pulsatile tablets were examined. Powdered ten tablets in a fine manner. Weighing the powder precisely allowed us to determine the necessary amounts to equal 20 mg of drug. And moved to a volumetric flask holding 100 mL. The flask had been packed with buffer and carefully blended. The resolution was fictitious. Both filtered and of Volume. Amount of resultant solution must be diluted: 1 ml to 100 ml Using medium, gauge the resultant solution's absorbance at utilizing a UV spectrophotometer [81].

### 11.1 IN VITRO EVALUTIONS

### 11.1.1 IN VITRO DISOLUTION STUDY

Using a paddle type (USP type II) dissolving apparatus (TDT-06P, Electro lab, Mumbai, India), the in vitro dissolution investigation was conducted. For the in vitro dissolution investigation, 500 mL of 0.1 N HCl (containing 0.5% (w/v) Tween 80) was used for the first two hours of the dissolution of the coated tablet, and then 900 mL of pH 6.8 phosphate buffer (containing 0.5% (w/v) Tween 80). The dissolving media was kept at 37±0.5 °C with a paddle speed of 75 rpm. Five millilitres of material were extracted and subjected to UV-visible spectrophotometer analysis at various intervals. Five millilitres of brand-new matching medium were added to the dissolving vessel each time the media was removed The appropriate wavelength was utilized for sample analysis since the MKS demonstrated maximal absorbance at wavelengths of 385 and 345 nm in 0.1 N HCl and phosphate buffer pH 6.8, respectively.

### 11.1.2 WATER UPTAKE STUDY

Under drug release test conditions, the pulsatile release tablets' water uptake was investigated. The media consisted of 0.5% (w/v) Tween 80 in 0.1 N HCl for two hours and 0.5% (w/v) Tween 80 in phosphate buffer pH 6.8 for a further two hours, or right up until the rupture time. Three pulsatile release pill weights were measured at predefined intervals and recorded against time. In Vitro Explosion Time Analysis The time point at which the outer coating burst was observed (n = 3) through visual inspection of the pulsatile release tablets in a USP type II (paddle) apparatus at 37 °C and 75 rpm of rotation in various fluids. This is known as the bursting time. The impact of media ionic concentration, pH, surfactant types and concentrations, and bursting time were investigated. The USP was followed in the preparation of the various pH 1.2, 4.5, 6.8, and 7.4 media. Visual observation was used to calculate the coated tablet's bursting time in various pH media.

A variety of media were made with the electrolyte mentioned in molar concentrations of 20, 50, and 100 mM. The medium's pH was then brought to 6.8 using either 1 M HCl or 1 M NaOH. Visual observation was used to calculate the coated tablet's bursting time in various medium. The media of pH 6.8 were prepared as per USP. The effect of different surfactants (SLS and Tween 80) in different concentrations (0.1, 0.2, 0.5, and 1.0 % (w/v)) on bursting time was observed by visual observation. The bursting time of optimized formulation in dissolution media was determined [medium 0.1 N HCl (with 0.5 % (w/v) Tween 80) for 2 h and phosphate buffer pH 6.8 (with 0.5 % (w/v) Tween 80)] in USP type II (paddle) apparatus at 37 °C, rotation speed 75 rpm.

### 11.1.3 THILNESS

All batches' thickness tables displayed thickness values between 2.7±0.3 and 3±0.5 mm [82].

### 11.1.4 DISINTIGRATION TIME

The tablet's disintegration time increased following coating with an impermeable anionic polymer. As the percentage of polymer coating grew, the disintegration time increased as well; conversely, it decreased as the concentration of sodium starch glycol-ate increased. For one hour, the tablet did not break down or exhibit any cracks in the simulated stomach fluid. Subsequently, the disintegration time increased from 181 to 384 minutes.

### 11.1.5 STABILTY STUDY

Over the course of a month, the stability studies conducted on the optimal formulation showed no discernible changes in the assay, drug release, lag time of the active medication, or the formulation's physical appearance [83].

### 11.2 IN VIVO EVALUTION

### 11.2.1 IN VIVO STUDY OF DRUG

In animal rooms with constant power and water supply, twelve healthy, white, healthy rabbits of both sexes weighing between two and three kilograms were chosen. They were kept at room temperature, 25°C, with a relative humidity of 45%, and fed a standard diet and water on demand.

### 11.2.2 IN VIVO STUDY DEGINE

Two groups of six rabbits each were randomly assigned. One group received the improved formulation F10 of pulsatile nimodipine tablets. (Group A) and the individual receiving pure medication was an equal dose to the other group (Group B) weight of an animal. Half a millilitre of blood. At 0, samples were taken from the marginal vein of the ear. 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 20, and 24 hours following the dose. Samples of blood should be combined with heparin and Centrifuged in a cooling centrifuge at 5000 rpm for five the plasma was isolated and kept at -minutes.
For additional analysis, 20°C [84].

## CONCLUSION:

In conclusion, the exploration of Chrono modulated drug delivery systems represents a captivating journey into the intersection of circadian biology and pharmacotherapy. The potential advantages, coupled with the clinical applications and ongoing research, underscore the significance of this innovative approach. While challenges persist, the evolving landscape of Chrono modulated drug delivery promises a paradigm shift in the way we administer therapeutics. As we navigate the intricate temporal dynamics of diseases and drug responses, the integration of Chrono-pharmacokinetics and the design of tailored delivery systems herald a future where treatment regimens are not only effective but also precisely synchronized with the rhythm of life.

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