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Chrono Therapeutic Drug Delivery Systems:An Emerging Strategy For Disease Specific Treatment Optimization

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ABSTRACT

A chronotherapeutic drug delivery system matches the release of drug to body's natural rhythms to enhance treatment outcomes and reduce side effects. By aligning drug administration with the timing of disease symptoms and metabolic processes, these systems enhance therapeutic efficacy. Advances in this field include time-controlled, pulsatile release formulations that target specific times of day. Such systems have shown promise in managing conditions like asthma and hypertension. Future developments aim to refine these systems further, leveraging smart materials and personalized approaches to optimize their effectiveness and safety in clinical settings.

Key Words: Pulsatile drug delivery systems, Circadian rhythms, Therapeutic efficacy, chrono biology

INTRODUCTION

The suprachiasmatic nucleus (SCN), the body's primary circadian regulator, regulates the body's own circadian rhythms[(2)]. Oral drug delivery systems dominate the global market by providing sustained therapeutic effects through controlled drug release within the therapeutic window[(1)]. In some cases, a delay before releasing a drug is advantageous, and pulse drug delivery systems release the drug after a specified lag time, which improves patient adherence. It is critical to have a lag time for targeted drug delivery to the colon, since it protects the drug from degradation in the acidic stomach environment, minimizes first-pass metabolism, and protects the drug from being degraded by stomach acidity, thereby enhancing bioavailability. Additionally, various bodily functions, including metabolism, behaviour, sleep cycles, and hormone secretion, are controlled by circadian rhythms[(3)]. Studies indicate the likelihood of experiencing heart attacks is higher in the early part of the day, with elevated cortisol amounts and circulatory pressure in the morning compared to lower levels at night. Nocturnal asthma often worsens in the early morning hours, and there is a sudden increase in gastric acidity at midnight. Additionally, cholesterol synthesis is higher at night compared to daytime. These circadian rhythm-related events underscore the need for designing time-specific drug delivery systems[(4)].

Chronobiology:
Chronobiology is the field focused on understanding biological rhythms and their underlying mechanisms. It includes the study of three primary types of rhythms in the body:

1.Circadian Rhythms: These are cycles lasting about 24 hours that control processes like sleep-wake patterns and hormone secretion[5].

2.Ultradian Rhythms: These rhythms occur more frequently than once per day, such as the 90-minute sleep cycles or periods of alertness and fatigue[6].

3.Infradian Rhythms: These rhythms have a longer than 24 hours, such as the menstrual cycle, which typically lasts about 28 days[7].

Desirable qualities for chronotherapeutic drug delivery systems should include:

- **Synchronize with Current Biomarkers:** Tailor the delivery system to specific biomarkers associated with the disease state.
- **Be Biocompatible and Biodegradable**: Ensure that the system is safe for the body and breaks down into non-toxic components.
- **Minimize Toxicity**: Avoid harmful effects from the delivery system itself.
- **Adapt to Circadian Rhythms**: Feature self-regulating and adaptive mechanisms that synchronize with the body's natural rhythms[8].

Chronotherapy:
Chronotherapy involves coordinating medical treatment with biological rhythms to optimize drug dosing at the most effective times of day. This approach enhances treatment efficacy and minimizes undesirable side effects by aligning medication administration with the body's natural rhythms.

Advantages:

- Reduced Dosage Frequency
- Better Patient Compliance
- Fewer Side Effects
- Enhanced Biological Tolerance
- Stomach Protection
- Efficient High First-Pass Drugs Delivery
- Targeted Site Delivery
- Predictable Release
- Increased Bioavailability
- Less Dose Dumping
- Improved Stability[9]

Limitations:

- Minimal Drug Dosage
- Partial Drug Release
- Variability in Drug Absorption
- Need for Skilled Personnel
- High Cost

IMPACT OF CIRCADIAN RHYTHMS ON PHARMACODYNAMICS AND PHARMACOKINETICS

Chronopharmacodynamics:
Biological rhythms at the cellular and subcellular levels can lead to notable variations in how medications affect the body depending on the timing of administration, independent of pharmacokinetics.

Absorption of drug:
Circadian rhythms can significantly affect the absorption of drugs taken orally by humans. Variations in gastric acid production, pH levels, gastrointestinal motility, rate of gastric emptying, and blood flow in the

digestive tract throughout the day time can influence absorption of drug. For example, variations in pH can alter the ionization of a drug based on its physical and chemical properties, affecting how well a drug is absorbed. Lipophilic drugs are particularly sensitive to these circadian variations, while hydrophilic drugs show less variation. Additionally, drug absorption via non-oral routes will be impacted by circadian cycles.

Distribution of drug:
Diurnal variations in bodily fluids and tissues can affect medication distribution throughout the day. Blood flow, influenced by the sympathetic and parasympathetic nervous systems, exhibits circadian patterns with increased sympathetic activity during the day and decreased activity at night. This diurnal variation in blood circulation and regional tissue perfusion can lead to differences in medication distribution based on the timing of dosing. **Furthermore, plasma proteins such as albumin and alpha-1-acid glycoprotein** also show circadian fluctuations, which can impact drug binding and distribution.

Metabolism of drug:
Liver drug metabolism is influenced by liver enzyme activity and blood flow in the liver, both of which display circadian fluctuations. Enzyme activity in the liver, kidney, and brain, among other tissues show time-dependent differences throughout the day. Chrono pharmacological studies have explored these temporal variations by examining the circadian patterns of drug metabolism and its metabolites. Processes like conjugation, hydrolysis, and oxidation are affected by these circadian rhythms. For instance, circadian fluctuations leads to variations in cytochrome CYP3A activity which is reflected in the urine 6β-hydrocortisol to cortisol ratio.

Elimination of drug:
Circadian fluctuations are observed in renal functions, including glomerular filtration, renal blood flow, urine pH, and tubular reabsorption, generally peaking during the daytime. These circadian changes can affect drug excretion in the urine. For example, variations in urinary pH can influence drug ionization, leading to faster excretion of acidic drugs if administered in the evening, as shown with sodium salicylate and sulfasalazine[10].

PULSATILE DRUG DELIVERY SYTEMS

Gastro-resistant systems:
Gastro-resistant systems have historically been designed to stop a drug from being released in the stomach. These systems are sensitive to pH changes and release the drug only when the pH exceeds 5 in the intestinal fluid. These systems are used for timed drug delivery, such as in Night time respiratory distress treatment. An salbuterol formulation utilizes a dual-coated core: initially coated with HPMC (hydroxypropyl methylcellulose) and subsequently with Eudragit® L30D, an enteric coating polymer. The delay period before drug uptake can be adjusted via varying the depth of the HPMC coating[11].

Multilayer formulations:
This type of systems use one or two polymer coatings, either impermeable or semi-permeable, applied to both sides of a core. A three-layer tablet was created for Dual-phase drug release, with two layers that contain the drug and a swellable polymer intermediate layer. The outer layer is coated with an impermeable polymer for delayed release. The initial layer might also include a hydrophilic layer without drug for an extended onset. The Geomatrix® system, a multi-layer tablet, features a hydrophilic matrix core and is used in Parkinson's treatment. This system reduces nocturnal and dawn symptoms, allowing for lower daily doses and 40% greater bioavailability compared to traditional controlled-release formulations[12].

Scheduled detonation systems:
This type of systems, used for individual and repeated dosage forms, feature a drug containing core, an osmotic compound, along with disintegrants. Covered with a shielding and partially permeable membrane, water influx causes osmotic pressure to build, leading to an explosive drug release. The delay period can be regulated by adjusting a specific outer polymer coating's thickness, and swelling agents can also facilitate the release.

Sigmoidal drug delivery systems:
This type of sustained release systems use an organic acid with osmotic properties to control drug release. These pellets are coated with an insoluble polymer to create a delay in drug release, known as the response time. By adjusting the coating depth, the lag period or response time can be extended up to 5 hours. After this delay, the rate at which the drug is released is not influenced by the coating thickness[13].

Compression-coated systems:
These systems are also known as press coated systems. The method is easy and cost-effective, involving core and coating compressed directly. Hydrophilic cellulose derivatives are commonly used, making laboratory-scale compression straightforward. However, for bulk production, specialized instruments are required. A main drawback is the need for substantial amounts of coating material[14].

Table 1: CLASSIFICATION OF CHRONOTHERAPEUTIC DRUG DELIVERY SYSTEMS:

Single unit system	**Capsular system**: It comprises a water-resistant capsule containing the drug and a cross-linked hydrogel plug that expands in gastrointestinal fluids, pushing the drug out of the capsule [15].
	Port systems: It consists of cellulose acetate membrane, an impermeable plug, and an osmotically active component combined with the drug in a gelatin capsule. Upon intake of gastric fluid, the inner pressure increases, causing the blocking component to be expelled upon a delay.
	Delivery by solubility modulation: The osmotic device facilitates pulse release by reducing the amount of sodium chloride required to maintain a saturated fluid state [16].
	Delivery by reservoir system: In chronotherapeutic drug delivery system, a barrier layer covers the reservoir. This layer degrades post a set delay time, allowing the drug to be quickly released from the core.
Multi-particulate system[17]	**Reservoir with rupturable polymeric coating:** The drug is first coated onto nonpareil seeds, then covered with a layer that expands and a top layer that does not dissolve. Dissolution rate and absorption rate studies show that scheduled-release explosion systems have a 3-hour delay period before the drug appears in the blood, with maximum release occurring after 5hours [18].
	Pulsatile delivery by change in membrane Permeability: Drug release is facilitated by alterations in the permeability of a polymeric coating layer when specific counter ions are present in the surrounding medium.
	Sigmoidal release systems: The system consists of pellets containing acids like succinic, acetic, glutamic, malic, and citric acids, coated with an ammonia methacrylate copolymer. Water penetration converts the core containing drug to an acidic formulation, which enhances the passage through the Water-saturated polymer film[19].
	Low density floating multiparticulte pulsatile systems: The drugs with an optimal absorption area in the stomach, buoyant with decreased density microparticle burst-release dosage forms facilitate prolonged drug presence in the stomach, minimizing the effects of acidity changes and gastric evacuation.
Stimuli induced pulsatile release system	**Temperature induced system:** Water-absorbing gels experience significant temperature induced reversible volume changes. N-isopropylacrylamide is the most popular polymer for consuming due to its extensive applications [20].
	Chemical stimuli induced pulsatile release: These systems are designed to release medications in reaction to biological factors such as enzymes, pH levels, or chemical signals. Such as, a gel made from poly-N-isopropylacrylamide with phenylboronic acid moieties exhibits significant swelling changes in the presence of monosaccharide [21].
	pH sensitive drug delivery systems: pH-dependent polymers control release of drug within specific ranges of pH. For example, phthalates, carboxymethyl cellulose, and methacrylic acid are used, with polymers like Eudragit L and S being particularly effective for colon targeting [22].
External stimuli induced	**Electrically stimulated Pulsatile system:** Applying an electric field to a rate-controlling membrane embedded with polyelectrolytes boosts the release of the drug [23].
	Magnetically stimulated Pulsatile system: Incorporating magnetic materials like magnetite, iron, nickel, or cobalt into capsules or tablets allows for controlled drug positioning and release. By applying an external magnetic field, the drug can be directed to specific locations [24].

	Ultrasonically stimulated Pulsatile system: Ultrasound improves the ability of drugs to pass via physiological barriers like skin by interacting with tissues. The mechanism involves absorbing acoustic energy, which causes oscillating bubbles. This results in non-thermal impacts like Electromagnetic pressure, Light-induced torque, and Sound-induced fluid motion, enhancing delivery of drugs [25].

Table2: Characterization of chronotherapeutic drug delivery system

S.No.	Parameter	Procedure
1	Tablet dimension and girth	Determined by measuring the thickness and diameter with Vernier calipers.
2	Hardness kg/cm²	Six randomly selected tablets are tested using a Monsanto hardness tester
3	Friability	Place a pre-weighed sample of tablets in a friabilator, rotate it at 25 rpm for 4 minutes (or 100 rotations), then reweigh the tablets. The percentage weight loss should not exceed 1%.
4	Weight Variation	Weigh 20 tablets individually, calculate the average weight, and ensure each tablet's weight falls within the permitted deviation range for its category.
5	Content Uniformity	Assay the active ingredient in 10 tablets individually. The content of each tablet should be within 85-115% of the label claim [26].
6	Floating Lag Time	The duration required for the tablet to rise and float on the surface of the dissolution medium, measured at pH 1.2, 37 ± 0.5°C, with paddle rotation at 50 rpm.
7	Total Floating Time	The duration during which the tablet continuously remains afloat on the surface of gastric fluid at pH 1.2, 37 ± 0.5°C, with paddle rotation at 50 rpm[27].
8	*In Vitro* dissolution Studies[28]	Place the tablet in a dissolution apparatus with medium at 37°C, rotate at optimum speed, and collect samples at intervals to measure drug release.
9	Water Uptake Study[28]	Immerse pre-weighed tablets in water or simulated gastric fluid for a set time, then remove, blot to remove excess liquid, and reweigh.Calculate the water uptake percentage based on the weight increase
10	Swelling Index[29]	SI= (Wet weight–Dry weight/Dry weight) × 100

Table 3:Disease conditions,symtoms and route of drug administration

Table 4:Recent technologies in chronotherapeutic drug delivery system

Technology	**Proprietary Name: Dosage form**	**Therapeutic agent**	**Pathology**
Controlled-release technology	Uniphyl, ER Tablet	Theophylline	Chronic respiratory illness
Osmotic-controlled release technology	Covera, ER Tablet	Verapamil HCL	Elevated arterial pressure
CODOS	Verelan, E R Tablet	Verapamil HCL	Elevated arterial pressure
CEFORM	Cardizem, ER tablet	Diltiazem HCl, Verapamil HCl	Elevated arterial pressure
DIFFUCAPS	Innopran –XL	Propranolol, Verapamil HCl	Elevated arterial pressure
Physicochemical Modification of API	Pepcid, Tablet	Famotidine	Erosion/ Open sore
Physicochemical Modification of API	Zocor, Tablet	Simvastatin	Elevated cholesterol levels
Pulsys®	Moxatag, Tablet	Amoxicillin	Throat inflammation, Tonsil infection
TIMER^{RX}	Opana®, ER tablet	Oxymorphone	Analgesic medication
Pulsincap	Pulsincap	Dofetilide	Hypertension
Geoclock technology	Lodotra	Prednisone	Rheumatoid arthritis
SODAS	Ritalin LA	Methylphenidate	Attention deficit hyperactivity disorder and Narcolepsy
IPDAS Technology	Naprelan	Naproxen sodium	Rheumatoid arthritis
DDR Technology	DEXILANT™	Dexlansoprazole	Heartburn associated with non-erosive gastroesophageal reflux disease
TheriForms (3DP)	Zip dose	Spritam (Levetiracetam)	Epilepsy

Table 5:Recent patents in chronotherapeutic drug delivery systems:

Drug	Drug Delivery Systems	Patent title	Patent number	Jurisdiction	Year
Atomoxetine	Oral drug delivery system	Orally disintegrating tablets of atomoxetine [31]	US8747895B2	US	2014
NA	transdermal drug delivery	Portable drug delivery device including a detachable and replaceable administration or dosing element [32]	US RE46,217 E	US	2016
NA	Oral drug delivery system	Pulsatile drug release [33]	US9474719B2	EP, US, JP	2016
Amphetamine salts	Oral drug delivery system	Controlled dose drug delivery system [34]	US20180344669A1	US	2018
Guanethidine	Oral and nasal inhalation routes	Aerosol delivery systems [35]	EP2841138B1	EP	2020
NA	Parentral drug delivery system (intravenous)	syringe control assembly [36]	JP2022548113A	JP	2022
NA	Oral drug delivery system	Modified release pharmaceutical powder compositions comprising a gastric raft formation system with triggered pulsatile drug release [37]	CN 112004520B	CN, EP, US	2024
NA	Tablets	Formas De Dosificacion Terapeutica[39]	ES 2436523 T3	ES	2014
NA	NA	Chronotherapeutic Pharmaceutical Composition[40]	EP 2389174 A4	EP	2014
NA	NA	Chronotherapeutic Dosage Forms[41]	EP 1368005 B9 20140611	EP	2014
NA	NA	Controlled Release Delivery Device Comprising an Organosol Coat[42]	EP 2007360 B1	EP	2014

Pregabalin	NA	Controlled Extended Release Pregabalin[43]	WO 2016/187718 A1	WO	2016
NA	NA	Drug Delivery Composition	US 2019 0083399 A9 20190321	US	2019

CONCLUSION

Rapid advancements in delivery of drugs has resulted in development of chronotherapeutic systems, that release medication at the most effective time, location, and dosage within the body. These systems offer major improvements over traditional methods by providing time-controlled, pulsatile release, crucial for chronotherapy. While sustained and controlled delivery maintains therapeutic levels over extended periods, pulsatile systems are specifically designed to align drug release with circadian rhythms, enhancing treatment efficacy for diseases influenced by biological rhythms. Chronopharmaceutics, which focuses on the timing of drug administration, is essential for overcoming delivery challenges and improving patient compliance[30].

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