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Review Article

Chronopharmaceutics: An Overview

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ABSTRACT

Chronopharmaceutics is an significant branch of pharmaceutics concentrated on designing drug-delivery systems that release therapeutic agents according to biological rhythms and the time-dependent requirements of the body.[1,4,7] Circadian rhythms influence several physiological, biochemical, pharmacokinetic, and pathological processes, along with blood pressure, hormone secretion, gastric acid secretion, inflammatory activity, drug absorption, metabolism, and elimination. Consequently, maintaining a constant drug concentration does not always provide a constant therapeutic effect. Chronotherapeutic drug delivery systems (CDDS) overcome this limitation by synchronizing drug release with the time when disease activity or therapeutic requirements are foremost. This analysis characterizes the basic principles, classification, mechanisms, applications, advantages, and recent advances in chronopharmaceutical drug delivery. Major CDDS approaches comprises pulsatile, time-controlled, osmotic, stimuli-responsive, multiparticulate, site-specific, and programmable systems. These systems includes predetermined lag period followed by rapid, delayed, or controlled drug release. Important technologies such as OROS®, CODAS®, CEFORM®, DIFFUCAPS®, PULSINCAP® and three-dimensional printing-based systems. Their drug-release mechanisms involve diffusion, dissolution, erosion, hydration, osmotic pressure, polymeric barriers, and responses to physiological or external stimuli. Chronopharmaceutical systems have promising applications in diseases manifesting predictable circadian patterns, such as bronchial asthma, cardiovascular diseases, arthritis, peptic and duodenal ulcers, hypercholesterolemia, diabetes mellitus, cerebrovascular disorders, pain, sleep disorders, and cancer. Simultaneous drug availability with disease activity may enhance therapeutic efficacy, reduce unwanted drug exposure and adverse effects, decrease dosing frequency, and enhance patient compliance and adherence. Recent innovations in multiparticulate drug delivery, three-dimensional printing, personalized medicine, and automated drug-delivery technologies have additionally expanded the

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potential of chronotherapy. Incorporation of circadian biology with pharmacokinetics, pharmacodynamics, formulation science, and personalized medicine may support the development of safer and more efficient treatment strategies. Further research and well-designed clinical studies are mandatory to establish the therapeutic benefits and broader clinical application of chronopharmaceutical drug-delivery systems.[10,11,13,15]

INTRODUCTION

Chronopharmaceutics is a branch of pharmaceutics dedicated to the design and evaluation of drug delivery systems where drug release is incorporated with the biological requirements of specific diseases. Human physiological, biochemical, and pathological processes experiences anticipated shifts changes over a 24-hour period because of circadian rhythms that are closely affiliated with the sleep activity cycle and effected by genetic and environmental factors. These changes can influence normal body functions, disease intense and progression, drug concentration and response to therapy. Chronotherapeutics is an essential treatment approach in which drug the availability is timed to overlap with rhythmic pattern of a disease. It's main aim is to achieving the best therapeutic effect while minimizing the side effects by considering changes in disease symptoms, pharmacological sensitivity and pharmacokinetic properties. Drug absorption, distribution, metabolism, and elimination may change according to the time of administration, during that the sensitivity of target tissues may differ according to biological rhythms. The concept has historical foundations dating to 1814, when Joseph Virey advised administering opium late at night instead of daytime. A constant drug concentration does not certainly produce a constant pharmacological action due to receptor sensitivity, physiological functions, catalytic activity, hormone secretion, and other biological processes may differ with time. Disorders such as hypertension, asthma, peptic ulcer and arthritis show circadian variations. For example, osteoarthritis manifestation may become more difficulty in the evening, while rheumatoid arthritis commonly causes maximum pain and stiffness during the early morning. Cardiovascular incidences such as angina, myocardial infarction, and stroke also occur more regularly during morning hours. These results have driven to the development of time-controlled, pulsatile, triggered, programmed, & delayed-release drug delivery systems. This approach is highly advantageous in cardiovascular diseases, where specially designed preparations may be administered at bedtime and release drugs during the early morning. Time-released systems have been established for drugs such as verapamil, diltiazem, and propranolol. The scientific basis of chronopharmaceutics is biological rhythms, particularly circadian rhythms, which follow approximately a 24-hour cycle. The circadian timing system is affected by environmental factors such as light, which is passed through the retina to the suprachiasmatic nucleus (SCN). By delivering the suitable amount of drug at the specific time, chronotherapeutic approaches can enhance therapeutic outcomes, increases patient tolerance, and minimize adverse effects.[4,7,9,11,12][15,17,18]

Circadian rhythms:

Circadian rhythms are innovate processes that follow a roughly 24-hour cycle in humans, animals, plants, and microorganisms. It is controlled by the circadian clock and modulated by the pattern of light and darkness. The rhythms are found in most physiological processes the sleep-wake cycle, hormone production, digestion, metabolism and gastric acid secretion.[1-4,7,10][17,18]

Chronotherapeutics:

Chronotherapeutics is a pharmaceutical approach is designed to optimized drug efficacy and minimization of adverse effects by the appropriate administration of medication formulated in relation to the time of day when disease or symptoms of a disease occur.[1-4,7,10] [13,14,17,18]

Chronotherapy: Chronotherapy is a therapeutic method that is based on the timing of drug administration and is related to circadian rhythms. It synchronizes drug administration with normal body function or with the cyclical onset of symptoms of a disease.[1-4,7,10] [13,14,17,18]

Chronobiology:

Chronobiology is the biology of time. It studies pattern in the life cycles of organisms and the connection between the patterns and environmental factors.

Chronobiology explores the relation between time and physiological processes in living organisms. The term chrono comes from the greek word for time, and biology studies life and its forms.[1-4,7,10][17,18]

Chronopharmacokinetics:

Chronopharmacokinetics is the study of the variation over time of the processes of absorption, distribution, metabolism and excretion of a drug. The main reason why chronopharmacokinetics is relevant is that the time which a drug is administered can modify the drug concentrations in the blood and tissues over time. Variations in diurnal rhythms in gastric acid secretion, gastrointestinalmotility protein binding, hepatic metabolism, renal blood flow, and urine pH, and excretion of drugs can contribute to these differences.[1-4,7,10] [13,15,17,18]

CLASSIFICATION OF CHRONOPHARMACEUTICAL DRUG DELIVERY SYSTEMS

The principal approaches used in CDDS include time-controlled, pulsatile, delayed-release, site-specific, osmosis, multiparticulate, stimuli-responsive, and programmable systems. The selection of a specific approach depends on the pharmacokinetic properties of the drug, disease rhythm, desired lag time, gastrointestinal physiology and therapeutic objective. Many pathological conditions do not exhibit steady-state symptoms throughout a 24 hour period. Instead, diseases like asthma, rheumatoid arthritis, hypertension follow predictable circadian variations so that chronopharmaceutics devices incorporate a predetermined lag time (a period during which no drug is released)[4,-7,9,11][13-16,19]

1. Pulsatile Chronopharmaceutical Drug Delivery Systems

It may depend on the time or dose in this, drugs are released in a controlled manner. Pulsatile DDS are one of the most important approaches in chronopharmaceutics. They are characterized by a lag phase via by rapid drug release of drug, producing a release of a drug pulse at a scheduled time. This release pattern can be beneficial when continuous exposure of drug is unnecessary and when therapeutic efficacy depends on the administration during a specific window of the day.

Pulsatile DDS are classified as follows:

Single Pulse Systems: They are engineered to release entire dose of a drug at one specific time after a predetermined lag period. They may be valuable when a single therapeutic peak is required during the dosing intervals.

Multi Pulse Systems: They incorporate multiple drug containing units or compartments scheduled to release their drug contents staggered intervals. They may be useful when a disease displays more than one period of increased activity during the day.

Time Controlled Pulsatile Systems: They are designed to maintain a predetermined period of minimal or zero drug release, before commencing drug delivery. The lag period can be regulated through the characteristics of coating, membrane, plug, or other rate-controlling components.

Site-Specific Pulsatile Systems: They integrate both temporal and spatial controls. Drug release takes place after the dosage form arrives at a particular GI region and encounters environmental conditions such as pH, enzymes or microbial activity.[4-7,9,11,12][15,16,19]

1. Time-Controlled Chronopharmaceutical Drug Delivery Systems

They are designed to maintain the drug in a non-releasing or minimally releasing state for a predetermined period before commencing drug release. This system is developed to ensure that the maximum drug concentration is available when the symptoms are expected to be the most severe. The lag time is an important formulation rules and can be adjusted by altering the composition, thickness and physicochemical characteristics of the release controlling barrier.

Diverse mechanical pathways are used for the drug release such as diffusion, dissolution, erosion and osmotic pressure. The examples of this systems such as Polymer-coated dosage forms, reservoir systems, barrier-layer systems, compression-coated tablets and capsule-based formulations are various approaches for this system. The review by Bussemer et al. Specifically distinguishes time- controlled pulsatile systems from

site-controlled systems and describes time-regulated delivery as release after a defined period rather than release mostly in response to gastroenteric environmental conditions.[4-7,9,11,12][15,16,19]

1. Osmotic CDDS

Osmotic systems that use the osmotic pressure as the driving force for release of drugs over time. In this system water enters the dosage form through a semi permeable membrane and develops osmotic pressure that facilitates movement of the drug from the formulation the drug is released through an orifice.

Important osmotic approaches may include:

Push-Pull osmotic systems

Delayed -Pulse osmotic systems

Osmotic Elementary pump systems

Osmotic mechanism's can be combined with a lag-time barrier to obtain delayed or pulsatile drug release. [4-7,9,11,12][15,16]

1. Stimuli-Responsive CDDS

This systems are designed to deliver the drug at right time and under the right physiological conditions, making them useful for chronotherapy. These systems can undergo changes in swelling, degradation, permeability, dissolvability, or structure in response to a stimuli, ensuring in a controlled drug release.

The major types of stimuli may include

pH-responisve systems: These systems use polymers whose ionization, swelling, dissolution, or permeability changes with pH. They can therefore provide site-specific or delayed drug release within the GI tract.

Temperature-responsive systems: Thermo responsive polymers undergo changes in their physical properties at specific temperatures. These changes can be exploited to trigger drug release.

Enzyme-responsive systems: Enzyme-sensitive polymers or linkages can be degraded by enzymes present at specific anatomical sites. This provides an opportunity for site-specific drug release.

Light-responsive systems: Light-sensitive materials can undergo structural or chemical changes after exposure to an appropriate wavelength, allowing temporally controlled drug release.[4-7,9,11,12] [15,16]

2. Site-Specific CDDS:

They are designed to release the drug at targeted location within the GI tract at a scheduled time. The primary objective is to synchronize drug availability with the circadian patterns of disease and deliver the drug precisely, where it is most required.

The key gastrointestinal targets include:

Stomach

Small intestine

Ileum

Colon

These systems exploit variations in pH, microbial activity, enzymes, and GI transit to achieve targeted drug release. Site-specific delivery is especially important for diseases where the pathological process or the therapeutic target is confined to a specific region of the GI tract. The mechanism typically involves the oral dosage form passing through the stomach and small intestine, releasing the drug only after arriving the intended site, and after a present lag time.

Major types of systems include pH-dependent, pressure-dependent, time-dependent, enzyme and microflora-dependent, osmotic, pulsatile and multi particulate systems. These approaches can enhance drug effectiveness, reduce side effects, lower dosing frequency, and improves patient compliance.[4-7,9,11,12][13,15,16,19]

CHRONOPHARMACEUTICAL TECHNOLOGIES

1. OROS Technology

OROS: Osmotic-controlled Release Oral system

It is an osmotic drug-delivery technology in which ''Osmotic pressure generated inside the dosage form controls drug release through a small delivery orifice''

Mechanism: The dosage form reaches the GI tract then GI fluid contacts the semipermeable membrane and water slowly enters the system and the osmotic layer absorbs water. So that the osmotic pressure develops then the generated pressure pushes the drug containing

material toward the delivery orifice finally drug is expelled at a controlled rate.

Types:

1. Chronotherapeutic ORDS
2. Specialized ORDS

Examples: Covera-HS- Verapamil, Procardia XL, Ditropan XL, Concerta[4,6,9,12][15,16]

1. CODAS Technology

CODAS = Chronotherapeutic oral drug absorption system. CODAS is a multiparticulate chronotherapeutic system, particularly designed for "bedtime administration" and delayed drug release. Drug loaded beads are coated with a combination of water-soluble polymer and water-insoluble polymer.

Mechanism: The dosage form is administered, usually at bed time and GI fluid penetrates the polymer coating then the water-soluble gradually dissolves, The dissolution produces pores in the coating then the water-insoluble component continues to act as a barrier. After the predetermined lag period, drug begins to diffuse through the pores. The controlled drug absorption occurs during the desired time period.

Example: Verelan PM- Verapamil.[4,7,9,12][15,16]

2. CEFORM Technology

CEFORM technology is a multiparticulate drug delivery technology that produces uniform spherical microspheres using a "melt-spinning process". Drug and/or polymeric materials are processed under controlled thermal and mechanical conditions to produce nearly spherical micro-spheres.

Mechanism: The microspheres can be formulated can be or coated to achieve the following: Immediate release, Delayed release, Sustained release, Controlled release. Various types of microspheres can also be combined to produce a desired overall release profile.

Example: Cardizem LA - Diltiazem.[4,6,9,12]

DIFFUCAPS Technology

DIFFUCAPS is a multiparticulate, capsule based drug delivery technology incorporating a multiple drug loaded beads, pellets or granules designed to yield a specific drug-release profile. Instead of relying on one large tablet matrix, the formulation contains numerous individual drug-containing particles. Different particle types can be design to release drug at different rates or after different lag periods. The system may contain: Drug-loaded beads, Pellets, Granules, Coated particles. The particles can be individually coated to attain different release characteristics.

Release patterns: Immediate release, sustained release, Delayed release, pulsatile release, and predetermined lag time. Lag periods of approximately 3-5 hours.

Example: InnoPran XL- Propranolol.[4,6,9,12]

1. PULSINCAP Technology

Pulsincap is a "Pulsatile DDS" designed to release the drug after a predetermined lag period. It is particularly useful when the drug should be release as a rapid pulse at a specific time after the demonstration. Atypical Pulsincap consists of drug-containing capsule body. Hydrogel plug, water-soluble cap, and often an enteric coating.

Mechanism:Whenever the dosage form is administered. The enteric coating when present protects the system from gastric fluid. After entering the appropriate GI region, fluid reaches the capsule then the water enters the system. The hydrogel plug absorbs water, plug wells. After a predetermined period, the swollen plug is pushed out. The drug is rapidly released.

Example: Glibenclamide.[4,6,9,12]

DISEASES AND THEIR TREATMENT

The main purpose is to synchronize drug release with the time at which the disease is most active, symptoms are most severe, or the drug is required at a particular site of the gastrointestinal tract. During the lag period, little or. no drug is released; after the predetermined time, the formulation produces a rapid or pulsatile release of the drug. [4-7,9,11,12]

The need for CDDS arises because disease activity, physiological functions, drug absorption, metabolism and elimination are not always constant throughout the day. Many biological processes follow approximately 24-hour circadian rhythms. Gastric acid secretion, gastrointestinal motility, hormone secretion, enzyme activity, blood pressure, heart rate and several disease symptoms can vary according to the time of day.

Therefore, giving the same dose at the same time with a conventional immediate- release or sustained release preparation may not always provide the best therapeutic response. [1-4,7,10]

1. Bronchial asthma

Asthma symptoms commonly worsen during the night and early morning. Airway resistance can increase during the night, and biological mediators involved in bronchoconstriction can show time-dependent changes. The increase in airway resistance during night-time and increased histamine release during the early morning period.[1,4,6,10]

The CDDS is very useful in the treatment of the asthma, if a conventional immediate-release bronchodilator is administered only after the patient develops severe symptoms, the drug is being given after the pathological process has already intensified.

The release pattern of CDDS is:

Bedtime administration → No/low drug release during early night → Predetermined lag time → Drug release before or around the period of greatest asthma symptoms →Bronchodilation.[4-7,9,11,12]

This approach can provide therapeutic drug levels when bronchoconstriction is expected to increase, potentially reducing nocturnal and early-morning symptoms. Drugs such as β2- agonists and antihistamines are the drug categories relevant to chronotherapy for asthma, with examples including albuterol, terbutaline, fexofenadine, cetirizine and loratadine.[1,4,6,10]

1. Peptic and Duodenal ulcers

Gastric acid secretion is highly crucial in the chronology therapy of peptic and duodenal ulcers. During the night, gastric acid secretion increases, while gastric activity, gastric emptying and intestinal movement may become slower. These changes can influence the disintegration, dissolution and absorption of orally administered medicines.[1,4,6,10]

The CDDS is useful to suppress acid secretion during the period when excessive acid production and ulcer-related symptoms are expected. Instead of maintaining a high concentration of an anti-ulcer drug throughout the entire day, a formulation can be designed to provide drug release at night.[1,4,6,10]

The release mechanism of the CDDS is:

Bedtime administration → Lag time → Night-time drug release → Suppression of excessive gastric acid secretion → Reduction of ulcer symptoms.

H_2-receptor antagonists such as cimetidine and famotidine are for peptic ulcer chronotherapy, while proton-pump inhibitors such as omeprazole and lansoprazole are associated with duodenal-ulcer treatment.[4-7,9,11,12]

2. Cardiovascular Diseases

Blood pressure is generally lower during sleep and rises rapidly around awakening. This early-morning increase in BP is commonly indicates as the morning blood-pressure surge. The source also describes increased platelet aggregation and decreased fibrinolytic activity during the morning, driving to a more hypercoagulable state.[1,4,6,10]

Myocardial infarction and other cardiovascular events have been reported to occur more frequently during the morning, particularly during the period following awakening. Increased sympathetic activity, catecholamines, cortisol, vascular tone and platelet aggregation are among the factors associated with this period.[1,4,6,7,10]

The drug release mechanisms are:

Night-time administration → Predetermined lag time → Drug release near early morning → Therapeutic drug concentration during morning get elevated.

Cardiovascular chronotherapy include:

Calcium-channel blockers, ACE inhibitors, Nitroglycerine

Examples: diltiazem, amlodipine, lisinopril, enalapril and nitroglycerine.

3. Arthritis

In rheumatoid arthritis, pain and stiffness typically become prominent in the morning. In contrast patients with osteoarthritis may experience greater pain during the night. In rheumatoid arthritis, inflammatory markers such as C-reactive protein and interleukin-6 also exhibit time-dependent variations.

The drug release mechanisms are:

Night-time/bedtime administration → Lag period → Drug release before morning → Increased drug availability during morning inflammatory symptoms → Reduction of morning pain and stiffness. [1,4,7,9,11,12]

NSAIDs such as ibuprofen, ketoprofen and diclofenac, and glucocorticoids such as prednisone.

4. Diabetes Mellitus

Insulin therapy aims to reproduce the physiological pattern of endogenous insulin secretion. Standard insulin secretion consists broadly of a basal component together with increased secretion linked to meals. Therefore, insulin delivery needs to correspond to changing metabolic requirements.[1,4,6,10]

PDDS and site-specific delivery

An additional challenge occurs with protein and peptide drugs such as insulin. Such molecules may be unstable in the upper gastrointestinal tract because of proteolytic enzymes. The source describes the colon as a potentially useful absorption region because proteolytic activity can be relatively lower than in the upper gastrointestinal tract.

A time-controlled formulation can be formulated to avoid premature release in the stomach and small intestine and release the drug after an appropriate lag period corresponding approximately to the time required for the dosage form to reach the colon.[4-7,9,11,12]

The release pattern of drug:

Oral administration → Protection from upper GIT → Transit through stomach and small intestine → Predetermined lag time →Colon arrival → Drug release.

5. Cancer

Cancer treatment is also an important area for chronotherapy because both tumor biology and normal tissue physiology can exhibit circadian variation.

The timing of chemotherapy can influence both therapeutic activity and toxicity. Tumor blood flow can also vary with the circadian cycle. This creates the possibility of selecting a drug-delivery time when the tumor may have a more favorable physiological environment for drug exposure.[1,4,7,10]

The release pattern of drugs is:

Drug administration at selected time → Predetermined/controlled release → Greater drug exposure during favorable tumor phase → Potentially improved antitumor effect → Reduced exposure/toxicity during vulnerable normal-tissue phases.[1,4,6,10]

Anti cancer drugs include:

Alkylating agents, Antimetabolites, Antimicrotubular agents

Examples include cisplatin, methotrexate, vincristine and vinblastine.

Advantages of Chronopharmaceutics

Improved Therapeutic Efficacy

Chronopharmaceutics can improve the effectiveness of treatment by matching drug release with the daily pattern of disease activity. Many body functions, such as heart function, lung activity, hormone release and metabolism, change during the 24-hour cycle. Changing the drug release according to these changes can help make the drug available when its action is needed most. [1,5-7,9,10]

Reduction in Adverse Effects and Toxicity

The effect and harmful effects of some drugs may change depending on the time they are given. Chronopharmaceutical systems can reduce drug exposure during times when treatment is less needed and release the drug during the proper treatment period. This time-based drug delivery help reduce unwanted side effects and maintain a better balance between benefits of the treatment and harmful effects caused by the drug.[1,5-7,9,10]

Reduced Dosing Frequency

Controlled-release chronopharmaceutical systems can keep drug levels in the body for a longer time and can reduce the need for taking the medicine frequently. A once-daily dose is more convenient than taking several doses in a day and may help patients follow their treatment properly.

Better Control of Disease Symptoms

Many diseases show regular changes in symptoms during the day. Chronopharmaceutical systems can be

designed to release the drug before or during the time when symptoms are expected to become worsen. This helps provide the right amount of drug in the body at the needed time and may improve control of disease symptoms. [1,5-7,9,10]

Improved Patient Convenience and Adherence

Reducing the number of doses taken each day and releasing drug according to the patient's treatment needs can make the treatment easier. A simple dosing schedule can help patients to follow their prescribed treatment more easily, especially when drug needs to work for a longer period. Systems that reduce the need for repeated doses may therefore help to improve patient adherence to the treatment.[1,4-7,9,10]

Optimized Pharmacokinetic Profile

Chronopharmaceutical systems can control the time and rate at which a drug becomes available in the body. By controlling when the drug is released and how fast it becomes available, the drug exposure can be adjusted according to treatment needs. Choosing the right drug delivery system may help achieve a suitable pharmacokinetic profile and improve the overall management of the treatment.[1,4-7,9,10]

Improved Disease Management

By considering the body's natural rhythms and changes in disease activity, chronopharmaceutics can provide a better approach than fixed dosing schedules for conditions where symptoms change at specific times. Matching drug release with the times when treatment is most needed may improve symptom control, treatment effectiveness, and overall management of the disease. [1,5-7,9,10]

RECENT ADVANCES IN CHRONOPHARMACEUTICS AND PULSATILE DRUG DELIVERY SYSTEM

Chronotherapy is a way of giving medicines when they are given, often to as timing treatment. planned in according to the internal biological of the body of the patient rhythm.[1-4,7,10][13,14,17]

Administering a medicine at the time when it is likely most effectively can boost its effects. This means they have a therapeutic effect, but reduce the risk of side effects.

More clinical trails are necessary to understand the potential of chronotherapy and provide guidance to its use. Expansion for regular implementation in clinical use. Advances in research and technology can continue to occur and quite, possibly, will continue to occur, which is why it is important to keep the ball rolling.

Pulsatile drug delivery systems are important for use in conditions where the drug needs to be delivered in a pulsatile fashion not regularly instead of a continuous release image. They are particularly applicable to illness like diabetes, where therapy could have to coincide with changing physiological requirements. Multiparticulate preparations, including pellets, are available for: several benefits over single-unit dosage forms. These include a lower risk of dose dumping, the ability to combine units with different release characteristics, and a relatively short and reproducible gastric residence time that is reproducible.[10,11] [13,15,18,19]

Whether the formulation is to be retained in the stomach for a longer period, gastroretentive systems are available. Release in the upper gastrointestinal tract. Successes in the Floating drug delivery systems. Some of them are: (FDDS), bioadhesive systems, and low-density porous multiparticulate preparations are among the methods used for this purpose.

Control-IQ is an advanced hybrid closed-loop system designed to support patient with diabetes manages insulin treatment. The system employs a mechanism that is activated in response to anticipated glucose delivers insulin accordingly and automatically adapts insulin deliver.. It could be rise, fall, or temporarily rise interruption of basal insulin release based on compatible integrated continuous readout. An (iCGM) and an ACE pump. Boluses for correction are possible in the system as well. When the glucose is anticipated to rise to a certain level. Its function is to decrease the matches the insulin requirements of the individual. Reduce the burden on patients and carers day to day deliver insulin to the patient more closely aligned to their insulin needs is similar to normal pancreatic control. Control-IQ is designed for use in the treatment of Type 1. Diabetes mellitus in people six years old and older.[1,4,6-10]

Future Aspects

1. Personalized chronomedicine: Integration of individual chronotype assessment (via genetic testing or wearable biosensors) to customize dosing time rather than applying a population-average schedule.[10,11][13,15,18]
2. Wearable- and app-integrated "smart" delivery systems: Devices that track circadian biomarkers (activity, temperature, heart rate variability) and adjust or remind patients of optimal dosing windows in real time.[10,11][13,15,18]
3. AI and machine learning-guided chronotherapy: Predictive models using patient physiological data to optimize dosing schedules and formulation design.[10,11][13,15,18]
4. Nanotechnology-based chronodelivery: Nanoparticles and liposomes engineered with stimuli-responsive coatings for more precise time- and site-specific release.[4-7,9,11,12][13,15,18]
5. 3D-printed chronopharmaceuticals: On-demand, patient-specific multilayer tablets with programmable lag times, enabled by additive manufacturing.[10,11][13,15,16]
6. Expansion into chrono-oncology and chrono-immunotherapy: Greater exploration of timing for immune checkpoint inhibitors and biologics to enhance efficacy and reduce immune-related adverse events.[10,11][13,15,18]
7. Regulatory evolution: Development of standardized guidelines and IVIVC frameworks specific to pulsatile/chronotherapeutic dosage forms to support faster clinical translation.[10,11][13,15,18]

CONCLUSION

In recent years the effectiveness, safety, and toxicity of numerous drugs has been shown to vary in relation to time of administration may change from one day to the next. These variations are associated with the circadian patterns of biochemical, physiological, and behavioral processes, with daily changes for disease symptoms and drug pharmacokinetics. Thus, it is important to understand the biological rhythms, provides an important scientific basis for chronotherapy.[1-4,7,10] [13,14,17,18]

From a pharmaceutical point of view, the treatment of this condition can be enhanced by giving traditional tablets and capsules at suitable doses and at the time or with specially engineered drug delivery systems which release medicines that can be in accordance with the biological clock of the body. Pulsatile, time-controlled, programmed, and externally triggered drug-delivery systems have been developed to produce the levels of drugs at the time that they are most required. Using body-worn ambulatory pumps and other advanced technologies is also undertaken to treat various different types of time-specific treatments.[4-7,9,11,12] [13,15]

Chronopharmaceutical systems are potentially beneficial in conditions such as asthma, cardiovascular disorders, arthritis, and other diseases in which symptoms or disease activity shows variation in the day. Selecting the appropriate dosing time can enhance therapeutic effects, minimize negative impacts, enhance patient safety, and boost adherence to treatment. These systems may also used for the delivery of proteins and other biological medicines, but not yet enough. Experimental, clinical and commercial research is needed.

The research of clock genes and cyclic biological markers can contribute to the determination of the best time for the use of these substances. Time for giving individual medicines the monitoring of these markers may enable treatment to be modified based on a patient's physiology and disease pattern. However, changes or mutations of clock genes can disrupt normal biological functions and can have serious effects on health.[1-4,7,10,][13,17,18]

As a result, there is a link between clock genes and biological rhythms. The response of the organism to rhythms and drug should be further investigated. Although it is desirable to keep the drug level at an optimum, this is not always possible in the body. If symptoms of disease and sensitivity to drugs follow a circadian rhythm, then the timing of drug release should be changed over time. Further research in chronopharmacology and chronotherapeutics is still needed. It is therefore important to find more effective and patient treatment strategies that are safer.[1-4,7,10] [13,19]

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