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Review Article

Chronotherapeutic Pulsatile Drug Delivery Systems in the Management of Type 2 Diabetes Mellitus: Advances and Future Perspectives

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ABSTRACT

Chronotherapeutic delivery of drugs has also become a potential approach to enhance therapeutic results by timing drug release in accordance with circadian rhythms of the body. Pulsatile drug delivery systems (PDDS) are uniquely intended to offer a programmed lag phase with subsequent rapid drug delivery so that they could be well utilized on diseases with time-dependent pathophysiology, including type 2 diabetes mellitus (T2DM). This review reveals that circadian variation plays a role in glucose metabolism and insulin secretion and that chrono pharmacological methodology can be of significance in managing diabetes. Several types of pulsatile delivery technologies are mentioned using capsular systems (e.g., Pulsincap), osmotic systems, rupturable coatings, and multiparticulate formulations, which are discussed in regard to their mechanisms and applications. Innovations like stimuli-responsive systems, smart polymers, and incorporation with digital health technologies have also increased the accuracy and reliability of PDDS. Though all this has happened, there are still issues of reproducibility, complexity of manufacturing and a lack of clinical validation. The future outlooks the creation of customized, glucose-sensitive delivery systems coupled with continuous glucose monitoring and artificial intelligence enabling improved therapy. All in all, PDDS is an innovative and efficient method of time-controlled drug delivery and glycemic control in T2DM.

INTRODUCTION

T2DM is among the widely prevalent metabolic disorders in existence and it is a massive health issue in the world. The material becomes poor as the body is not able to produce or utilize insulin properly which results in high blood sugar and the damage of the heart, kidneys and nerves in the long run. Essentially, the current lifestyle and dietary behaviours, as well as aging population, are all

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increasing the incidence of T2DM and hence an effective cure is a global agenda.[1] Majority of individuals either use oral hypoglycaemic drugs or insulin injections to maintain the blood sugar levels at a normal level but they are typically tailored to a constant dose and they do not consider the day-to-day variation in our bodies. That can become challenging to keep pace with the changes in glucose metabolism that occur during the day in reality.[2] Due to that, there has been growing interest among many regarding drug delivery systems able to be programmed to release drug based on biological processes of the body so that a person can achieve better results. The human body follows a 24-hour cycle which is to a great extent controlled by suprachiasmatic nucleus under the hypothalamus. The hormone release and the metabolism as well as sleep-wake is regulated by that inner clock. It goes even as far as to pull on glucose homeostasis, liver glucose production, and insulin sensitivity. A disturbance in those rhythms is associated with conditions such as obesity and type 2 diabetes, which are the disorders of the metabolism.[1,2] There are common circadian variations in glucose levels manifested by diabetics. The example of a classic one is the dawn phenomenon, during which the level of blood sugar increases at the beginning of the morning due to hormonal fluctuations and the insulin cycle in the body. This indicates the significance of timing of taking drugs and this is why we should have therapies that can administer drugs at the time when the body requires the drugs most.[1] This issue has provided chronotherapy with much hype in the research of pharma. Chronotherapy simply involves using drug on schedule relative to disease rhythms in order to achieve optimal effect and minimise side effects. It is already showing promise with the conditions with circadian patterns, such as asthma, high blood pressure, arthritis, and naturally diabetes.[2] Among all strategies, one of them is the pulsatile drug delivery systems (PDDS). They are intended to wait a predetermined lag time after which they discharge the full dose in succession with nature, and solve the disease at an opportune moment. PDDS is perfect when you do not want the drug to work all the time but at a certain point. Pharma tech has created a number of oral pulsatile delivery means in the last few years (capsules, press-coated tablets, osmotic systems, swelling-controlled systems and multiparticulate pellets).[3] Pulsincap-like capsular systems have been intensively researched with regard to their programmable lag time and a high-rate release.[4] Such systems are supposed to allow us to regulate the emergence of the drug depending on the circadian variations in the course of diseases. The aim is to increase the efficiency of therapy, enhance patient adherence, and decrease the frequency of the doses in chronotherapy.[3,5] This comprises the basics of the chronotherapeutic delivery, the various oral PDDS technologies, the mediums and procedures of testing them, and how all this can be applied to the treatment of type 2 diabetes. The latest findings, the present-day issues, and the perspectives in the area of chronotherapeutic pulsatile drug delivery are discussed as well.[3]

METHODOLOGY

The review article has been created on the basis of a systematic and thorough search of electronic databases such as PubMed, Scopus, ScienceDirect and Google Scholar containing publications published during the period 2000-2025, with particular attention paid to the latest developments (2020-2025). The inclusion criteria were limited to peer-reviewed research articles, review papers and clinical studies, all in English. Critical analysis was done on articles that dwelled on formulation strategies, pulsatile release mechanisms, chronopharmacology of antidiabetic medication, and clinical relevance. The extracted data were

compared and synthesized to outline the existing trends, technology, constraints and future outlook in PDDS in diabetes management. To ensure that the quality and relevance of the review, irrelevant, duplicate and outdated studies were eliminated.

1. CIRCADIAN RHYTHM AND GLUCOSE HOMEOSTASIS

1.1.Circadian Regulation Molecular Mechanism

Circadian rhythms are just natural cycles of 24 hours that regulate half the planet of physiological and metabolic activities. The central pacemaker in the hypothalamus suprachiasmatic nucleus (SCN) plays the principal role in the maintenance of the breast of the clock in mammals. The peripheral clocks are everywhere within the body and they are important in glucose homeostasis because they control the time of metabolic gene expression as well as the secretion of hormones.[6] These rhythms are molecular-based and facilitated by transcription-translation feedback loop which works with core clock genes. CLOCK and BMAL1 initiate PER and CRY genes; the proteins accumulated by the genes feedback, and inhibit CLOCK-BMAL1 activity. There is also the hormonal homeostasis which is closely circadian regulated and this is glucocorticoids, insulin, among other metabolic hormones which maintain the balance.[7] Research indicates that the clock is capable of controlling such processes as glucose uptake, gluconeogenesis and glucagon metabolism. Chemical activities are synchronized with our every-day eating and starvation rhythms by these oscillations. When you manipulate these clock genes, metabolic dysfunction that predisposes people to obesity, or type 2 diabetes can be observed.[8,9]

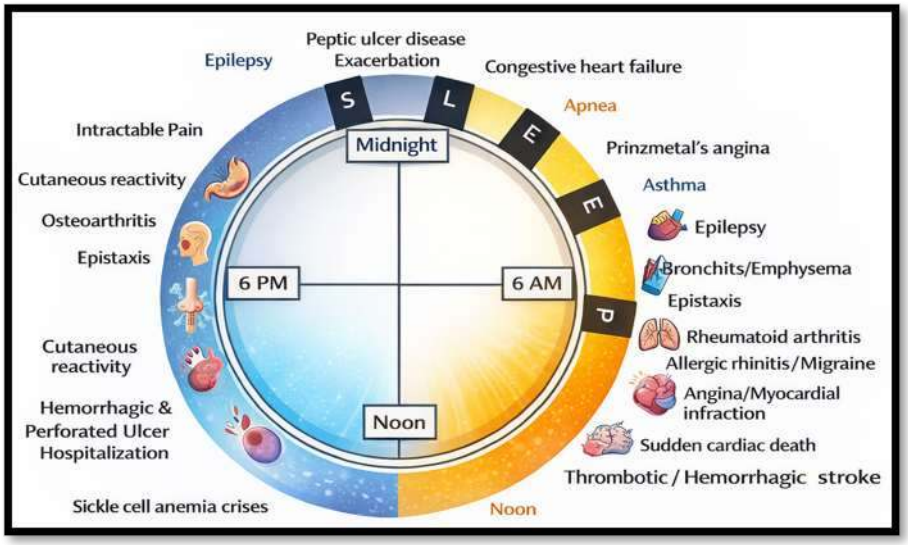

Figure.1: Cycle of Circadian Rhythm

1.2.Circadian Variation in Insulin Secretion

Insulin secretion and glucose metabolism have an apparent circadian oscillation throughout the day. The secretion of insulin is adjusted to our fasting-feeding orations in order to maintain the blood sugar concentration constant. Pancreatic beta cells possess their small clocks that synchronize the oscillatory expression of the insulin-production, insulin- secretion, glucose-sensing genes.[10] They have discovered that the insulin sensitivity and glucose tolerance vary with the time of the day-usually it is quite high during the morning compared to at night. The reason is that the release

of insulin and the peripheral sensitization is controlled by the circadian rhythms. Sleep and circadian rhythms have an enormous role in the glucose regulation as well; insulin sensitivity and glucose tolerance may be reduced by the lack of sleep or circadian disruption.[11]

In a recent randomized controlled clinical study (2024) in night-shift workers, the effects of circadian disruption on the insulin sensitivity and glucose metabolism were revealed. Those who were exposed to circadian misalignment in this study had a considerably lower insulin sensitivity and glucose regulation than when it was aligned. Also, melatonin administration enhanced insulin sensitivity and circadian rhythmicity, which is a direct indication of the biological clock control of glucose homeostasis and insulin secretion. These results are excellent clinical arguments that disruption to circadian rhythms has a detrimental impact on insulin dynamics and glucose tolerance, and that chronobiological regulation is crucial in the control of metabolism.[12]

1.3.Dawn Phenomenon in Type 2 Diabetes

In human beings with diabetes, the morning glucose peak is known as the dawn phenomenon and typically occurs between 4:00am and 8:00am. This increase does not stem from low night time blood sugar levels but is associated with hormonal fluctuation during the early morning. Liver glucose production is increased by the nighttime surge of growth hormone; an anti-insulin hormone. Large quantities of growth hormone generated within a sleep may aggravate insulin-resistance and initiate morning hyperglycaemia. Glucose metabolism is also a tweaker of other circadian rhythm hormone such as cortisol and catecholamines. Various causes of increased severity of the dawn phenomenon among type-2 diabetics comprise defective secretion of insulin and amplified insulin resistance that result in the continued morning hyperglycaemia and a lack of capability to maintain the level of blood glucose.[13]

In a post-hoc analysis of a randomized controlled trial, Wang et al. (2021) observed that the rise in the dawn phenomenon was 35.9+-17.9 mg/dL of nocturnal glucose nadirs of 123.9+-40.7 mg/dL in 50 adults with type 2 diabetes (aged 53.5+-8.2 years, HbA1c 8.4+-1.2) who had previously taken metformin. Glibenclamide (n=23) had no effect, but administering acarbose (n=27) substantially reduced this to 28.3+-16.5 mg/dL (p=0.037) and decreased the mean amplitude of glycaemic level fluctuations to 71.4 mg/dL. These results highlight the benefits of alpha-glucosidase inhibitors in addressing circadian irregularities and the association connecting the dawn phenomenon and daily glucose changes.[14]

2. CHRONOTHERAPY PRINCIPLE OF DIABETES MANAGEMENT

2.1.Chronotherapy and Chrono Pharmacology of Antidiabetic Agents

Chronotherapy in diabetes aims at matching drug use with the circadian rhythms with the goal of maximizing therapeutic effect and reducing adverse effects. The temporal changes in physiological activities, including the secretion of insulin, the tolerance to glucose, the production of hepatic glucose, and hormone control play a significant role in the pharmacodynamics and pharmacokinetics of antidiabetic agents. Chronopharmacology specifically studies the effects of these biological rhythms on drug absorption, distribution, metabolism and excretion, which results in time-dependent changes in drug response. In type 2 diabetes, the decreased insulin sensitivity at night time and the elevated hepatic glucose synthesis in early mornings indicate the role of timed drug administration. Properly timed intake of

antidiabetic medications can aid in the enhancement of glycemic control, elevate drug response, and decrease chance of hypoglycemia. Therefore, by incorporating the concept of chronopharmacology into the therapeutic approaches, it will be possible to manage diabetes in a more specific and more physiologically aligned way.[15]

2.2.Time Specificity of Drug Administration:

The time-release delivery technologies have become a defining modality in the improvement of the diabetes therapy. These systems are designed to convey pharmacological agents where intervals are preset to coincide with circadian intervals in glucose metabolism perturbation. These strategies come in especially handy in the reduction of such phenomena as early-morning hyperglycaemia also known as the dawn phenomenon.[16] Pulsatile drug delivery systems and chronotherapeutic formulations have a predetermined lag time in order to generate desired drug release so that optimum therapeutic concentrations occur during periods of physiological need. This model increases patient compliance, increases glycemic attitudes, and reduces negative incidents related to standard dosing schedules.[15] Overall, the concept of chronotherapy has a great potential in the management of diabetes through the coordination of the pharmacotherapy with the natural biological rhythms of the body which enhances treatment efficacy and physiological homeostasis.

3. OVERVIEW OF PULSATILE DRUG DELIVERY SYSTEMS (PDDS)

3.1.Concept and Major Characteristics

Pulsatile drug delivery systems (PDDS) are novel drug delivery systems that release the active pharmaceutical ingredient rapidly in a pulse format upon a set lag time, as opposed to a continuous release. They are especially useful in the treatment of diseases with circadian regulation, the symptoms of which vary over time, e.g. diabetes, asthma, and hypertension. PDDS are able to synchronize drug delivery to biological rhythms, so that therapeutic levels can be attained when the body is at peak demand.[17] The given approach helps improve the therapeutic efficacy, decrease the exposure to unnecessary drugs, and decrease adverse effects. Its defining feature is that it is characterized by a defined lag period during which there is little or no release of drugs, followed by one sharp and complete release pulse, and this is done by capsular system, osmotic devices, rupturable coatings, and plug-based systems that can be used to accurately control when the drug is released.[18,19]

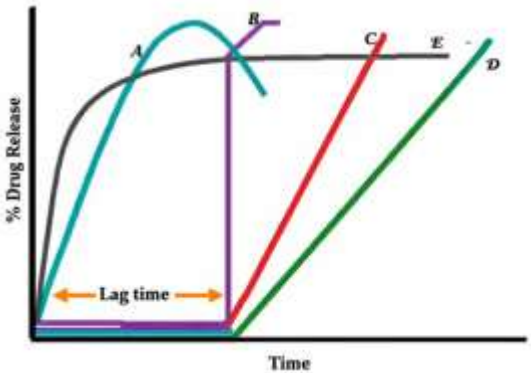

Figure.2: Drug release profile from PDDS vs. conventional vs. delayed release

Where, A: Conventional release profile, B: Burst release of drug after a lag time, C: Delayed release profile after a lag time, D: Constant release profile in prolonged period after a lag time, E: Extended-release profile without lag time.

3.2.Pulsatile over sustained release systems

- Offers drug release on a time control that is in line with the circadian rhythm of illnesses.
- Increases the treatment efficacy by releasing the drug at the peak of symptoms.

- Cuts down the tolerance of drugs and tachyphylaxis due to prolonged drug exposure.
- Increases patient compliance as a result of lower dosing schedule.
- Applicable to drugs with short half-life which need frequent ingestion.
- Applicable in treatment of diseases that are chronotherapeutic like asthma, hypertension, arthritis and diabetes.

4. ORAL PULSATILE DRUG DELIVERY TECHNOLOGIES

The purpose of oral pulsatile delivery systems is to administer drugs in a time regulated form after a preset delay then adopt a rapid release of the drug.[20] Such systems have been applied specifically in the treatment of the ailments that display circadian rhythms whereby the symptoms become evident at a given time of the day.[21]

Table 1: Pulsatile drug delivery technologies and its mechamism[21]

SYSTEM	MECHANISM	KEY FEATURES
Capsular-Based Systems	Drug is contained in a closed capsule body with a hydrogel/polymeric plug which swells or erodes on contact with GI fluids resulting in plug expulsion and release of drug fast after a lag time	Minimal design, manufacturing, fine control of lag time, chronotherapy.[22]
Rupturable Coating Systems	Drug core is covered with a polymer layer which breaks on the internal pressure caused by swelling or osmotic agents after penetration by fluids.	Sharp burst release, adjustable lag time through coating thickness and composition.[23]
Soluble/ Erodible Membrane Systems	The Outer polymeric coating (e.g., HPMC or lipid layer) dissolves or erodes with time, regulating lag phase prior to drug release.	Lag time is dependent on coating thickness and viscosity; easy and predictable release mechanism.[24]
Osmosis-Based Systems	Drug release due to osmotic pressure created by the inflow of water through a semipermeable membrane after a threshold is met or through an orifice.	Controlled and reproducible discharge, to some extent regardless of GI conditions.[25,26]
Multi-Unit Pellet Systems	Multiple drug-loaded pellets whose polymer coatings have varying lag times give staggered lag times, which leads to sequential or multiple pulse releases.	Dumping of reduced dose, even distribution of GI, flexible release profiles, better safety.[22]

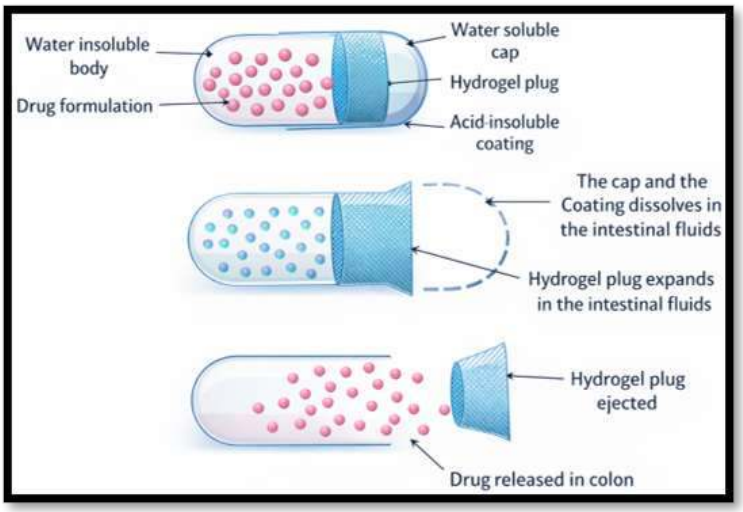

Figure.3: Capsular-Based Systems[22]

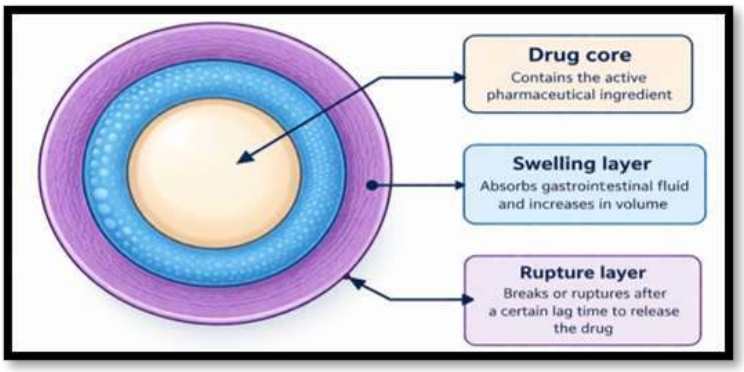

Figure.4: Rupturable Coating Systems[23]

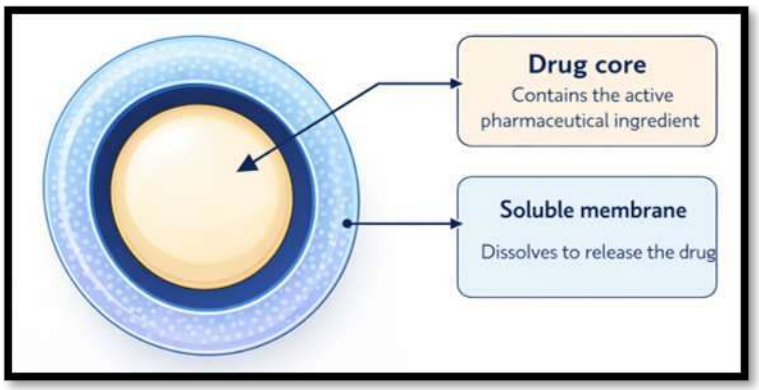

Figure.5: Delivery system with soluble or erodible membranes[24]

5. APPLICATION OF PULSATILE SYSTEM IN TYPE 2 DIABETES

- PDDS allow the synchronization of drug delivery with circadian rhythms to enhance treatment efficacy and decrease adverse effects in T2DM.[27]
- Clinically, it is of importance to target the dawn phenomenon (early morning hyperglycemia), which is both linked to higher HbA1c and worse glycemic control; time-specific interventions have demonstrated a reduction in glucose excursions.[28]
- Therapy-circadian glucose peak synchrony enhances insulin sensitivity and glucose metabolism, because biological timing is a critical factor in glucose homeostasis.[28]
- The use of chronotherapy to administer drugs has shown to achieve better clinical outcomes in various diseases, such as being more effective and less toxic when used in accordance with circadian rhythms.[27]
- Recent discoveries (2023-2025) suggest that time-specific therapeutic and smart dosing strategies may further improve the glycemic control and treatment accuracy in diabetes management.[29]

6. CHALLENGES AND TRANSLATION BARRIERS

Although pulsatile drug delivery systems (PDDS) have strong potential in the chronotherapeutic management of type 2 diabetes, there are a number of challenges which restrict their translation out of the research to clinical practices. Such

impediments relate to complexity of formulations, biological diversity and regulation.

6.1.Manufacturing Complexity

PDDS has several steps of processing such as coating, encapsulation, and assembly of functional components making the production more complex than traditional dosage forms. Accurate manipulation of factors like polymer formulation, coating depth and mechanical strength is needed in order to obtain desirable drug release characteristics.

Expanding such systems beyond laboratory to large-scale production also poses other issues such as batch-to-batch variation, large cost of production and specialized equipment. All these factors have the potential to constrain large-scale manufacturing and commercialization of pulsatile systems.[30]

6.2.Reproducibility of Lag Time

Consistent and reproducible lag time is a fundamental need of pulsatile systems of drug delivery. Nevertheless, the difference in formulation factors including polymer swelling, uniformity of the coating and plug integrity may cause discrepancies in timing of drug release.

In addition, physiological influences such as pH, motility, and fluid in the gastrointestinal system may alter the behavior of systems, leading to uncontrolled drug release. This inconsistency may undermine the success of chronotherapeutic treatment, in which time is of the essence.[31]

6.3.Circadian Variability in patients

Chronotherapeutic drug delivery depend on the alignment with the biological rhythms, yet circadian patterns are not the same as they vary in people with differences in lifestyle, sleep, age, and disease states. Circadian rhythms are usually disturbed in type 2 diabetes patients and cause disturbed glucose metabolism. This inter-individual difference complicates the process of developing one universal pulsatile system that is effective and works with all patients, highlighting the importance of individualized chronotherapy methods.[32]

6.4.Regulatory Considerations

The unique drug release mechanism and complicated structures make regulation approval of PDDS difficult. To show safety, efficacy, quality and reproducibility of such systems, regulatory agencies need a large amount of data. It is specifically challenging to determine in vitro-in vivo correlation (IVIVC), because the release of drugs is affected by the properties of the formulation and physiologically. Also, there are no particular regulatory recommendations concerning the chronotherapeutic systems, which can slow down the approval and commercialization procedures.[33]

7. RECENT ADVANCES IN PULSATILE DRUG DELIVERY SYSTEM

Recent advances in pulsatile drug delivery systems have been devoted to enhanced accuracy and reproducibility of lag time, involving both advanced polymer coating and multiparticulate delivery systems and stimuli-responsive delivery systems. These inventions allow a greater control of swelling, erosion or rupture-based release, leading to precise and predictable pulsatile drug delivery in contrast to conventional systems.[34]

Table 2: Recent advances Pulsatile technologies and its mechanism[34]

TECHNOLOGY	MECHANISM	APPLICATION
Accubreak Technology	The dosage unit is further subdivided into smaller units like mini-tablet or multiparticulate pellet and these are introduced into a controlled release system. The drug is enclosed after administration up to a pre-determined lag time. The outer membrane is ruptured as a result of swelling, osmotic pressure, or enzymatical activity and the drug is rapidly released.	Facilitates accurate lag time regulation and fast pulsatile release; can be used as a chronotherapeutic agent.[35]
TMDS Technology	A multi-component tablet system which is used to introduce more than one drug or drug fraction that releases at a varied rate in one dosage form.	Permits the optimization of numerous release profiles of ingredients; enhances therapeutic flexibility.
Geoclock Technology	An outer coating is an insoluble and non-elastic polymer mix which encloses the active drug core and the outer coating. This coating regulates lag time and release of drugs.	Chronic use (e.g., LODOTRA in rheumatoid arthritis); delayed and site-specific release.[36]
Duredas Technology (Dual Release Drug Absorption System)	Adopts a bilayer tablet structure where one of the layers releases the drug immediately and the other layer allows the drug to be released gradually or at a slow rate.	Co-delivers both immediate and prolonged release in one dosage form; enhances efficacy and adherence.
Innoherb Technology	Herbal drugs are converted into beads or pellets and encapsulated. A semi-permeable coating of membrane is used to regulate release and cover bad taste.	Fits well in herbal preparations; enhances taste suppression, and controlled drug release.[37]
Orbexa Technology	Granulation is employed to load drugs, then polymer coating is used to regulate drug release. Protein-based formulations can also be modified to this system.	Applicable to high-dose proteins and drugs; permits pulse release profiles.[38]

8. RESEARCH GAP AND FUTURE SCOPE

Regardless of the significant progress, there are still a number of important gaps in the clinical translation of the chronotherapeutic pulsatile drug delivery systems (PDDS) to treat type 2 diabetes. The majority of systems remain in preclinical studies, with little large-scale clinical data on their long-term safety and effectiveness.[39] Moreover, it is still hard to realize the same and reproducible lag time in vivo because of the variability of gastrointestinal physiology and circadian rhythms across individuals.[40] Legal obstacles, such as absence of standardized guidelines and poor in vitro-in vivo overlap (IVIVC) also hinder the development and commercialization of such systems.[41] Furthermore, existing formulations are not personal enough to deal with individual patient metabolic and circadian differences. Subsequent studies ought to then involve the creation of intelligent, glucose reactive delivery mechanisms blended with digital health technologies including continuous glucose sensors and wearable gadgets. The integration of artificial intelligence and machine learning of real-time data analysis and adaptive dosing also promise great potential in the development of individualized chronotherapy and a better glycemic outcome.[42]

9. CONCLUSION

The introduction of chronotherapeutic pulsatile drug delivery systems is an innovative and promising way of managing type 2 diabetes mellitus, whereby the release of drugs is synchronized with circadian changes in glucose

metabolism and insulin release. The systems have considerable benefits compared to traditional dosage forms, such as enhanced therapeutic effect, minimized side effects, and increased patient compliance. Pulsatile systems of capsular, osmotic pumps, multiparticulate formulations, and stimuli-responsive platforms have also enhanced the potential of PDDS to provide time-controlled drug delivery. Nevertheless, issues like variability in lag time, lack of clinical validation, and manufacturing complications have been some of the obstacles to extensive clinical use. The accuracy and efficiency of chronotherapy is likely to become more precise and effective with the integration of smart drug delivery systems with digital health technologies and the personalization of medicine methods in the future. In general, PDDS has great potential to revolutionize diabetes management by offering more physiological and patient-centric approaches to treatment.

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