

**Review Article**

**A REVIEW ON RECENT ADVANCEMENT IN PULSATILE DRUG DELIVERY SYSTEMS**

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**ABSTRACT**

Delivery systems with a pulsatile-release method are particularly involved in designing medicines for which traditional managed drug-release systems with the continuous release are not suitable. This medication also has a high first-pass impact or special conditions for chrono-pharmacology. These medications also have a high first-pass or unique chronopharmacological effect. The pulsatile release profile is characterised by a duration of no release (lag time) followed by a fast and full release of the drug. Pulsatile drug delivery systems may be classified into site-specific systems in which the drug is released inside the gastrointestinal system (e. g. colon) or time-controlled devices wherein the drug is released after a well-defined time period. Site-regulated release is typically controlled by environmental factors, such as pH or enzymes found in the intestinal tract, whereas drug release from time-controlled processes is controlled mainly by the delivery system and, preferably, not by the environment. This review covers various single-and multiple-unit oral pulsatile drug-delivery systems with an emphasis on time-controlled drug-release systems.

**Keywords:** Circadian, Pulsatile, Drug delivery, Advancement

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**INTRODUCTION**

The circadian behaviour of the disease helps the medicine to release in pulsatile form. Pulsatile forms of drug delivery systems are achieving a lot of interest as they deliver the medicine at a particular time to the actual sight in the right quantity, ultimately offering spatial extent and increasing drug user compliance. Pulsatile form of drug delivery system is defined as the fast and pulsative release of certain amount of active pharmaceutical ingredients molecule immediately, within a short time frame, and later a pre-determined off-release period. Thus, these systems are designed in such way that based on the body circadian cycle. Principle reasons for the use of pulsatile release of mechanism of action for drugs where a constant drug release, i.e. a zero-order release, is not necessary. To understand the circadian rhythm of the disease, first we need to understand the chrono-pharmacotherapy or chronotherapeutics. This term 'chrono' in essence to the observations that each and every anabolic and catabolic action go through the rhythmic alteration in time. Many hormonal, metabolic and other function of the body varies considerably in a day. These variations in body system reason alteration in diseased state and in the concentration of drug plasma drug in blood. Circadian rhythm is based on the daily routine which is also include sleep activity, and it is affected by modern gene structure of human and at the end it alters the body's function day and night. The reliance on bodily function in the circadian rhythm in certain disease is well known. Variety of hormone in large number released by brain during morning while different kind of hormones has been released sleeping at night. Blood pressure and heart rate of body are elevated between 6.00 am to 12.00 noon due to circadian rhythm of hormone release. The word "Chronotherapeutics" made up of 2 words, that is 'chronobiology' and 'pharmaceutics'. Chronobiology refers to biology branch which is concerned with the periodicity occurring in living creature. Many diseases follow circadian rhythm for example, hypertension, arthritis, peptic ulcer, asthma, neurological disorder, cancer, diabetes, hypercholesterolemia etc. Some of the above diseases are worse during the day for example, osteoarthritis while some of them are worse in evening and nights during sleep for example cough [1-3]. Current review covers various single and multiple-unit oral pulsatile drug-delivery systems with an emphasis on time-controlled drug-release systems and the recent advancement in pulsatile drug delivery systems

**Biological rhythm**

There are mainly three type of biological rhythm (period of oscillation,  $Dian=time$ )

**Infradian rhythm**

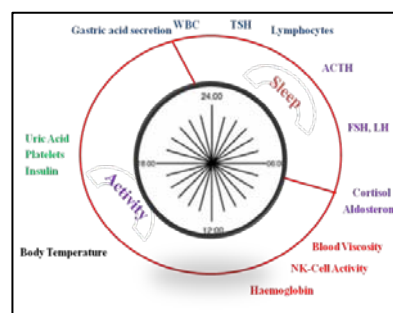
Oscillation which takes more than 28 h to complete is known as Infradian rhythm, for example-monthly menstruation.

**Ultradian rhythm**

Shorter cycle oscillations are named as an ultradian rhythm that is less than 20 h. In physiological processes, Ultradian rhythms were detected, like circulation, cellular cycles, periods of hormone release and sleep, respiration, as well as in behavioural functions, sometimes tied to patterns of feeding.

**Circadian rhythm**

Circa stands for circle and dian for time. Circadian rhythms are self-sustaining, occurring oscillations with a frequency of around 24 h. Such rhythms allow organisms to predict and plan for specific and periodic changes in the environment as shown in fig. 1 [4, 5].



**Fig. 1: Cycle of circadian Rhythm [4]**

**Classification of pulsatile system**

It is mainly in two forms, named as a single unit system and a multiple unit system as shown in table 1.

**Single unit system** is developed by the use of erodible or breakable coating on core material; it is either in capsule form or in osmotic based type formulation.

**Multiple unit system** generates pulsatile release by use of different permeability of membrane for coating of beads/core material [6-11].

**Table 1: Types of pulsatile drug delivery system [9, 10]**

Single unit system	Capsule based system Capsule based osmosis system Erodible or soluble barrier coating Pulsatile system with rupturable coating membrane
Multiple-unit system	Pulsatile system with a rupturable coating Osmotic based rupturable coating system Pulsatile Delivery by Change in Membrane Permeability

**Table 2: Types of pulsatile drug delivery system**

Time controlled system	Pulsatile System Based on Osmosis [9, 11] Pulsatile Delivery by Rupture of Membrane [11, 13] Capsule Shaped Pulsatile Drug Delivery System [11, 14]
Internally Stimuli Induced System	Temperature-induced pulsatile release Thermo responsive hydro gel systems [12, 13, 18] Thermo responsive polymeric micelle systems [14, 17, 19] Chemical stimuli induced pulsatile release Glucose-responsive insulin release devices [15] PH sensitive drug delivery system [15] Inflammation-induced pulsatile release [16] Drug release from intelligent gels responding to antibody [16] Concentration [16]
Externally Regulated System	Magnetic induces release [21] Ultrasound induces release [21] Light induces release [21] Electric field induces release [21]
Multiparticulate System	PRODAS Technology (Programmable Oral Drug Absorption System) [22] SODAS Technology (Spheroidal Oral Drug Absorption System) [22] CODAS Technology (Chronotherapeutic Oral Drug Absorption System) [21] DIFFUCAPS Technology [23] OROS Technology (Osmotic-controlled Release Oral delivery System) [9, 23]

### Types of pulsatile drug delivery system

As shown in table 2 various types of pulsatile drug delivery systems are as follows

#### Time controlled system

##### a) Pulsatile delivery by solubilisation or erosion of layer

In this type of delivery system the active drug ingredient release at the site of action where outer polymer layer start dissolving itself due to polymer solubilising property at that area of GIT. Release rate of active pharmaceutical ingredient is controlled by the thickness of coating layer [11-13, 21, 23].

##### b) Pulsatile delivery by rupture of membrane

Rupturing of the membrane is achieved by the use of such type polymer which is insoluble in water but water permeable, and the use of the effervescent or swelling agents. Water insoluble coating layer affect the lag time and lag time may alter by the thickness of outer layer [21, 23].

##### c) Capsule shaped pulsatile drug delivery system

In this type of pulsatile formulation, it contains an insoluble capsule. Plug is fitted within the capsule which creates two chambers in capsule body one is immediate release and other is pulsatile release chamber. The length of the soluble plug inside the capsule control the lag time of drug release [9, 13, 14, 16, 23].

##### d) Pulsatile system based on osmosis

In this, capsule is coated with semi permeable polymer and it contain insoluble plug which divided the capsule into parts. In capsule, one part contains active pharmaceutical ingredient and the other part contain osmotic agent. When drug is administered the GIT, fluid enter to the capsule through semi permeable side and osmogen create osmotic pressure which move the insoluble plug thus active drug release has achieved [16, 17, 19, 22].

#### Internally stimuli induced system

##### a) Temperature-induced pulsatile release

Thermal sensitive polymers or hydro gels are used to make these types of pulsatile release formulation. Temperature is mostly used

triggering signal for the release of the drug in the body. Body temperature is elevated by the pathogens or pyrogens which lead to alter the size of the hydro gels or polymers and this is followed by release of drug from reservoir [14, 17, 19, 22].

##### b) Chemical stimuli induced pulsatile release

In the chemical induced pulsatile system, such kind of polymers are used to develop formulation which alter their size or start solubilising itself when they meet the favourable criteria. For example, glucose responsive polymer, which contain insulin as core material. When glucose level increases in the body then glucose responsive polymer show response and drug released. Similarly, other polymers like pH sensitive, inflammatory responsive and other enzyme sensitive polymers are used to develop formulation [16, 18, 19, 24].

##### c) Externally regulated system

In this, the active pharmaceutical ingredient is contained in device and that device is implanted in the human body. Thus, that drug remains in device unless external signal is not given [23, 24].

##### Magnetic induces release

It contain magnetic beads along with copolymer matrix which is loaded with particular drug and are implanted in body. When the beads implanted area will exposure to the magnetic field then beads start oscillating and drug will release through the device [18, 19, 23].

##### Ultrasound induces release

Ultrasonounds are used to improve the permeation of some drugs in the body. Drugs are loaded in biodegradable matrix and to increase the degradation rate of the matrix to release drug at fast rate ultrasonounds are used [18, 23, 24].

##### Light induces release

In this type of formulation drug is mixed with such kind of material which absorb light of particular wavelength and that absorbed light helps to regulate release of drug through matrix. For example, Nano shells that absorbed light of near infra red light and generate heat through absorbed light of particular wavelength which leads to collapsing of hydro gels that enhance the release rate of drug through matrix [24].

**Electric field induces release**

These formulations contain polyelectrolyte or polymer which have number of ions in their backbone. Number of devices are used to perform chronotherapy, thus electric or pH sensitive polymer are used to formulate such kind of device because they alter their structure when they are exposed to external electric field and drug release achieved [15, 19, 24].

**Multiparticulate system**

It is capsular shaped drug formulation containing three parts that core material, coating material and binder or super-disintegrant. The goal of the multiparticulate dosage form design is to create a stable formulation that has all the advantages of formulating a single unit [19, 21, 24].

**CODAS technology (Chronotherapeutic oral drug absorption system)**

In this type of multiparticulate formulation, it contains drug beads coated with two polymers. Some beads are coated with water soluble polymer which released drug immediately and other are coated with water insoluble which show circadian release of drug

Example= Verelan PM XL capsule/Active Pharmaceutical ingredient-Verapamil HCl [24].

**SODAS technology (Spheroidal oral drug absorption system)**

These types of formulation comes under customised dosage form for particular patients' accordance of their need. Here few beads are coated with one kind of polymer and other beads are coated with different kind of polymer to achieve pulsatile release of drug [24].

**PRODAS technology (Programmable oral drug absorption system)**

It contain number of minitablets which are compressed together with active ingredient to form single dose unit. It may fill in capsule and control the rate release of drug [24].

**DIFFUCAPS technology**

It release drug in body in circadian manner. It contains core material inert which contain drug in its surrounding. Release rate can control by the thickness of coating material. Example= Innopran XL Tablets Verapamil HCl [24].

**OROS technology (Osmotic-controlled release oral delivery system)**

It is similar to the above formulation described in time-controlled system. It contains capsule body which contain plug that create two chambers in capsule. One compartment is filled by osmotic agent and other is filled by drug. Capsule is coated with semipermeable membrane. Osmotic pressure is created by osmogen and plug moved with to the side of pressure, this led to drug release through the second compartment which contain drug. Example= Alpress LP (prazosin), Covera-HS (Verapamil), Procardia XL [(nifedipine) [25, 26].

**Mechanism of action drug release from Pulsatile drug delivery system**

The active pharmaceutical ingredients release from pulsatile drug delivery system followed.

**Diffusion**

It is the process of movement of material from high concentration to low concentration. It does not require any energy for movement [27, 28].

**Osmosis**

It is the process of movement of drug particle from/material through semi-permeable membrane from low concentration to high concentration. In this process, movement require external energy which is created by osmogenes [25, 28].

**Erosion**

In this process the coating membrane start eroding itself with respect to time [26, 28].

Also some of the advantages and disadvantages of PDDS are shown in table 3 and 4 below.

**Table 3: Advantages of pulsatile drug delivery system [33, 34]**

S. No.	Advantages of pulsatile drug delivery system
1	Due to Its ability to release immediately at starting increase its absorption and bioavailability at the targeted site.
2	It limits the risk of mucosal irritation.
3	It decreases the loss drug which occurs due to first pass metabolism.
4	Less number of doses intakes without reducing its therapeutic effect as compare to conventional dosage form.
5	There is no effect of food in pulsatile drug delivery system, also GIT pH and fluid does not affect the dosage form because of use of such kind of polymers
6	No risk of dose dumping.
7	Drug interaction is decreased with the use of CYP450 isoenzymes.
8	Patient compliance increases as compare to conventional dosage form.
9	Due to novel drug delivery system undesirable side effects of drugs are avoided.
10	Flexibility in the design of pulsatile formulation.
11	Achieve a unique release pattern.

**Table 4: Disadvantages of pulsatile drug delivery system**

S. No.	Disadvantages of pulsatile drug delivery system
1.	Drug loading capacity is low.
2.	Production of pulsatile drug delivery system is expensive.
3.	Lack of manufacturing reproducibility and efficacy.
4.	Unpredictable in IVIVC.
5.	Advance technology required for production.
6.	Larger number of process variable.
7.	Trained or skilled person required to perform activities.

**Disease that required pulsatile drug delivery system**

Body biological process and functions are organized in the time of 24 h to conduct specific activity in particular time. Numbers of diseases are following the biological rhythm (table 5) [35, 36].

**Recent advancement in pulsatile drug delivery system**

At present, technology developing rate is high which is helpful for performing the experiments in large number with easy way and in less time. Thus, numbers of experiments were performed and

numbers of formulation are developed with high efficacy, bioavailability, stability and low risks [35-38, 42].

Some formulation to describe the advancement in pulsatile drug delivery system

**Table 5: Diseases that are diagnosed by pulsatile drug delivery system [35, 36]**

Time	Disease	Chronological behaviour	Used drug
6 pm, 12 pm	Peptic ulcer	Acid secretion is high in the afternoon and at the night	H <sub>2</sub> blocker
12 am 6 pm	Asthama	During night and early morning	B <sub>2</sub> agonist, antihistamine
12 pm	Arthritis	Pain increase at night	NSAIDs's, Glucocorticoids
---	Diabetes mellitus	Increase in blood after meal	Insulin, Sulfonyurea
8pm 4am	Hypercholesterolemia	Higher during at night as compared to day	HMG CoA reductase inhibitors
6 am	Cardiovascular Disease	Blood pressure reduce during the sleep cycle and start increasing at early morning	Nitro-glycerine, Calcium-channel blocker, ACE Inhibitors

#### ACCU-BREAK technology

In this technology, formulation splits itself to small tablets of exact dosage form, thus dose adjustment becomes simple. In ACCU-T-CR tri-layer tablets, tablets contain control release medication and immediate release ingredients [35, 36, 38].

#### T M D S technology

The time multiple action system provided control release rate of multiple ingredients within a single dose [40].

#### GEOLOCK technology

This technology contains press-coated tablet in which the active drug stays surrounded by an additional hydrophobic wax layer [40].

#### DUREDAS technology (Dual release drug absorption system)

Here bilayer tablets were manufactured. One layer released immediately and other layer release after some time which is predetermined [39, 40].

#### K V/24

In this, one or more drugs are remaining encapsulated to release drug in predetermine manner. Neutral core which is coated previously is again coated with drug to achieve drug release profile once a day [38, 40].

#### INNOHERB

It contains pallets coated with polymer and kept in capsule shell. It contains herbal compound [40, 41].

#### IPDAS technology (Intestinal protective drug absorption system)

It involve high density compressed form of drug with control release. Normally drug release immediately in GIT but to create control release of drug, bead matrix or semi permeable membrane are used. It comes under multiparticulate system [39, 40].

#### ORBEXA technology

It comes under multiparticulate in which high drug loaded and product is subject to granulation. After performing further process beads are created and coated with functional polymer [40, 41].

#### CONCLUSION

Reduction in drug intake is usually achieved by the discovery of the sustained/controlled drug delivery system and it gains too much attention due to its beneficence. This type of formulation release active drug to the particular site of action at right time, but it does not release active drug according to circadian manner. Due to advance technology and availability of all necessary requirements pharmaceutical field also grow at fast rate and develop such kind of formulation which release in particular manner by following the circadian behaviour of the body. Controlled/Sustained release drug delivery system are much way better than conventional dosages forms and Pulsatile form of drug delivery system have more advantages over sustained release formulations thus by comparing it with conventional dosages form will create great difference related to their advantages and disadvantages.

#### Future scope

As in some disease conditions, the prospect of chronotherapy and pulsatile delivery of drugs seems to be very optimistic in future. Pulsatile drug delivery strategies acquire time-controlled and site-specific dosage of single or multiple devices. Pulsatile flow in formulation is achieved by use of different kind of polymers and thickness of coating layer also control the rate release of active pharmaceutical ingredient.

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#### AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

#### CONFLICT OF INTERESTS

The Authors declare no conflict of interest, financial or otherwise.

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