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Time-Controlled Pulsatile Drug Transport: An Updated Review

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ABSTRACT
In current years, pulsatile drug release systems (PDRS) are ahead raising attention as compared to conventional drugs. Pulsatile drug delivery systems are developed to deliver drug according to circadian behavior of diseases. This means that these systems will deliver drug at time when disease display it's most morbid and mortal state within a circadian cycle (24 hrs.). The product follows a sigmoidal drug release profile characterized by a time period of no release (lag time) followed by a rapid and complete drug release. Thus, drug can be delivered at right time, in right amount and at right site of action by use of such approach. In this review the potential benefits of chronotherapeutic have been discussed for number of diseases like asthma, arthritis, cancer, diabetes, epilepsy, hypertension, ulcer, hypercholesterolemia etc. Various capsular, osmotic, single and multiple unit systems that are modulated by soluble or erodible polymer coatings, rupturable membranes are available in market. These systems are beneficial for diseases showing chrono pharmacological behavior where night time dosing is required or for the drugs having high first pass effect or having site specific absorption in GIT, or for drugs with high risk of toxicity or tolerance. These systems also improve patient compliance by decreasing dosing frequency.

KEYWORDS: Pulsatile, Circadian cycle, Chronotherapeutic, Hypercholesterolemia, Chrono pharmacological.

I. INTRODUCTION

Pulsatile release drug delivery system (PDDS) is defined as the timed release of drugs after programmable lag phases. Following the lag phase, drug release may be rapid and quantitative, lasting for a long time. Lag time is defined as the time it takes between placing a dosage form in an aqueous environment and the active ingredient starting to be released from the dosage form[1]. These pulsatile systems are gaining popularity as a means of developing drugs for which conventional controlled drug release systems with continuous release are ineffective. PDDS are gaining popularity because the drug is released fully after a defined lag time [2]. These pulsatile systems are useful for drugs with chrono- pharmacological behaviour where night time dosing is required, as well as for drugs with a high first pass effect and having an absorption site in the GIT. Pulsatile drug delivery systems can be time controlled (or) site-specific controlled [3]. Pulsatile drug delivery is defined as the rapid and transient release of certain amount of molecules within a short time period immediately after a predetermined off-released period, i.e., lag time or these systems have a peculiar mechanism of delivering the drug rapidly and completely after a lag time i.e., a period of no drug release. Such a release pattern is known as pulsatile release.[4]

II. CIRCARDIAN TIME STRUCTURE

Circadian rhythms are controlled by an inbred master clock network composed of the paired supra chiasmatic nuclei (SCN) that are sited in the hypothalamus and the pineal gland. This master clock network arranges the period and phase of the multitude of submissive peripheral circadian clocks located in cells, tissues, and organ-systems. The end effect is a rather exquisite temporal organization of biological processes and functions. Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 hours. Circadian rhythms are synchronized according to internal biologic clocks related to the sleep- wake cycle. Our circadian rhythm is based on sleep activity cycle and is influenced by our genetic makeup and thereby affects our bodies' function throughout day and night (24-hour period). Circadian rhythm regulates many body functions in humans like breakdown, physiology, behavior, sleep pattern, hormone production. There are number of conditions which show circadian pattern and advantage could be taken by timing and adjusting the administration of drugs according to the circadian rhythm of the disease. Compression coating is the absolute dry coating without solvent and heat use. The compression coated tablet dosage form (tablet-in-tablet design) is a time and rate-controlled drug delivery device, which consist of a

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core tablet and an outer layer that is considerably thicker than typical tablet core tablet and which completely, surrounds the core tablet. This method has no limitation for the cores & coating. This method can be used to protect hygroscopic, light sensitive, oxygen –labile or acid labile drugs, to combine and separate different drugs and to modify drug release pattern.[5,6,7]

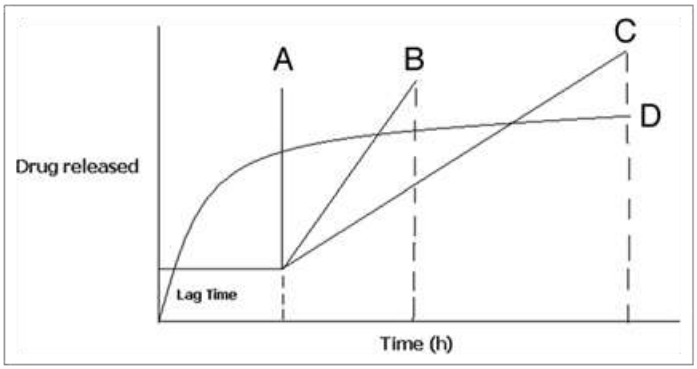

FIGURE 1. SCHEMATIC REPRESENTATION OF DIFFERENT DRUG DELIVERY SYSTEMS WHERE (A) SIGMOIDAL RELEASE AFTER LAG TIME (B) DELAYED RELEASE AFTER LAG TIME (C) SUSTAINED RELEASE AFTER LAG TIME (D) EXTENDED RELEASE WITHOUT LAG TIME.

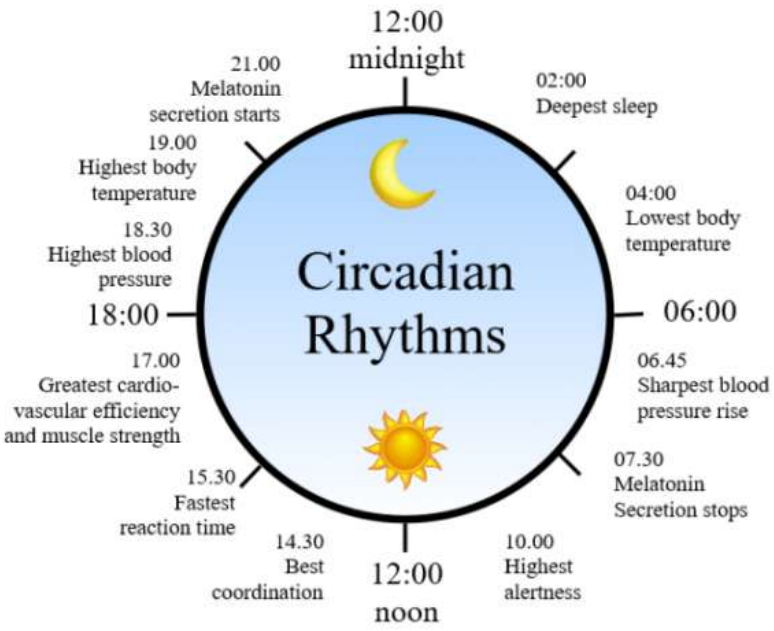

Figure 2. Cycle of circardian rhythm

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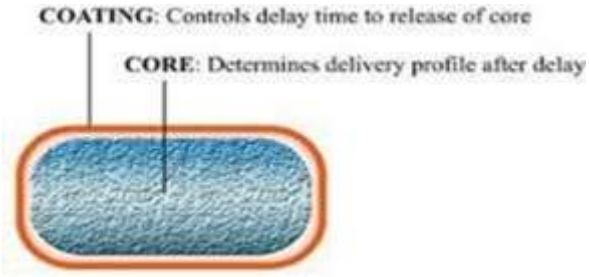

FIGURE 3. PULSATILE DRUG DELIVERY

III. NECESSITIES OF PULSATILE DRUG DELIVERY SYSTEM (PDDS)

1. First pass metabolism: Some drugs, such as beta blockers, and salicylamide, undergo extensive first pass metabolism and require fast drug input to saturate metabolizing enzymes in order to minimize pre-systemic metabolism. Thus, a constant/sustained oral method of delivery would result in reduced oral bioavailability.

2. Biological tolerance: Continuous release drug plasma profiles are often accompanied by a decline in the pharmacotherapeutic effect of the drug, e.g., biological tolerance of transdermal nitroglycerin.

3. Special chrono pharmacological needs: Circadian rhythms in certain physiological functions are well established. It has been recognized that many symptoms and onset of disease occur during specific time periods of the 24-hour day, e.g., asthma and angina pectoris attacks are most frequently in the morning hours.

4. Local therapeutic need: For the treatment of local disorders such as inflammatory bowel disease, the delivery of compounds to the site of inflammation with no loss due to absorption in the small intestine is highly desirable to achieve the therapeutic effect and to minimize side effects.

5. Gastric irritation or drug instability in gastric fluid: For compounds with gastric irritation or chemical instability in gastric fluid, the use of a sustained release preparation may exacerbate gastric irritation and chemical instability in gastric fluid.

6. Drug absorption differences in various gastrointestinal segments: In general, drug absorption is moderately slow in the stomach, rapid in the small intestine, and sharply declining in the large intestine. Compensation for changing absorption characteristics in the gastrointestinal tract may be important for some drugs. For example, it is rational for a delivery system to pump out the drug much faster when the system reaches the distal segment of the intestine, to avoid the entombment of the drug in the feaces [8,9]

IV. HIGHLIGHTS OF PDDS

1. These systems can be used for extended day time or night time activity.
2. They reduce the dose frequency, dose size and cost, which ultimately reduce side effects, thereby improving patient compliance.
3. Hormones such as renin, aldosterone, and cortisol etc. their levels in blood may alter with circadian rhythms therefore drug delivery through this system suits circadian rhythms of body functions or diseases.
4. Drug targeting to a specific site, like the colon (in case of ulcerative colitis) can be achieved.
5. This system helps to prevent the continuous presence of some drugs (e.g. salbutamol sulphate) that produce biological tolerance and thus they increase their therapeutic effect

V. CHALLENGES IN USING PDDS

1. Multiple manufacturing steps in case of multi particulate drug delivery system.
2. Low drug loading capacity and incomplete release of drug.
3. In vivo variability in single unit pulsatile drug delivery system.
4. Drug dose manipulation in case of child and elder patients is not possible.
5. Immediate withdrawal of drug is not possible. [10,11,12]

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Table 1. Diseases that require pulsatile drug delivery [11,12]

S. No.	Disease	Chronological behavior	Drugs used
1.	Peptic ulcer	Acid secretion is high in the afternoon and at night.	H_2blockers
2.	Cancer	The blood flow to tumors is threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase.	Vinca alkaloids, Taxanes
3.	Duodenal ulcer	Gastric acid secretion is highest at night, while gastric and small bowel motility and gastric emptying are all slower at night.	Proton pump inhibitors
4.	Neurological disorders	The central pathophysiology of epilepsy and the behavioral classification of convulsive events.	MAO-B inhibitor
5.	Hypercholesterolemia	Cholesterol synthesis is generally higher during night than day time.	HMG CoA reductase, Inhibitors
6.	Diabetes mellitus	Increase in the blood sugar level after meal.	Sulfonylurea, Insulin
7.	Arthritis	Level of pain increases at night.	NSAIDs, Glucocorticoids
8.	Cardiovascular diseases BP is at its lowest during the sleep cycle and rises steeply during the early morning.		Nitroglycerin, calcium channel blocker, ACE inhibitors
9.	Asthma	Precipitation of attacks during night or at early morning.	B_2 agonist, Antihistamines
10.	Attention deficit syndrome	Increase in DOPA level in afternoon.	Methylphenidate

VI. METHODOLOGIES FOR PULSATILE DRUG DELIVERY

Methodologies for the pulsatile drug delivery system can be broadly classified into three classes;

1. Time controlled
2. Stimuli induced
3. Externally regulated

1. Time controlled pulsatile release system: In time controlled drug delivery systems pulsatile release is obtained after a specific time interval in order to mimic the circadian rhythm. Such type of pulsatile drug delivery system contains two components: one is of immediate release type and other one is a pulsed release type.

Various methodologies that can be used for time controlled pulsatile release systems are following:-

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a. DELIVERY SYSTEMS WITH RUPTURABLE COATING LAYER:

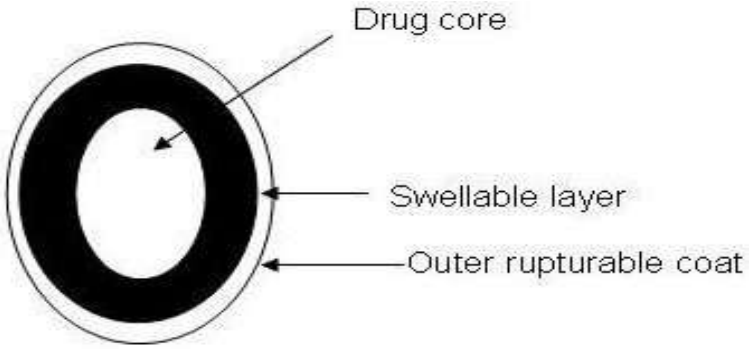

FIGURE 4: SCHEMATIC DIAGRAM OF DELIVER SYSTEMS WITH RUTPURABLE COATING LAYER

These systems consist of an outer release controlling water insoluble but permeable coating subject to mechanically induced rupture phenomenon. Recently different systems based on hard gelatin capsules and tablet core were described, all coated by inner swellable and outer rutpurable layer. The film rupture may be attained by including swelling, osmotic effervescent additives in the reservoir. By optimizing the system, drug release can be obtained at specific time interval. [13,14]

b. DELIVERY SYSTEMS PROVIDED WITH ERODIBLE COATING LAYERS:

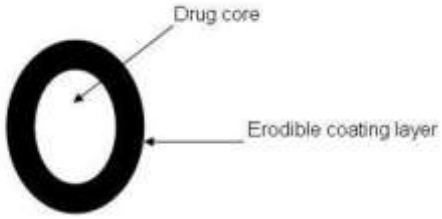

FIGURE 5: SCHEMATIC DIAGRAM OF DELIVERY SYSTEMS WITH ERODIBLE COATING LAYERS

In such systems the drug release is controlled by the dissolution or erosion of the outer coat which is applied on the core containing drug. Time dependent release of the active ingredient can be obtained by optimizing the thickness of the outer coat.

c. **CAPSULE SHAPED SYSTEM PROVIDED WITH RELEASE CONTROLLING PLUG:**

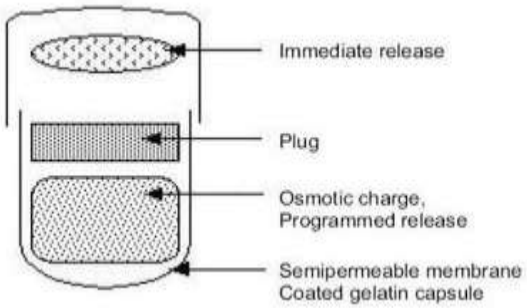

FIGURE 6: SCHEMATIC DIAGRAM OF CAPSULE SHAPED SYSTEM PROVIDED WITH RELEASE CONTROLLING PLUG

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These systems contain release controlling plug between immediate release compartment and pulsed release compartment. On contact with aqueous fluids, the cap rapidly dissolves thereby releasing the immediate release component followed by pulsed release component. The lag time is provided by the plug which is inserted in to the body.[15]

2. Stimuli induced pulsatile systems:

In these systems there is release of the drug after stimulation by any biological factor like temperature, or any other chemical stimuli. These systems are further classified as:

a. Temperature induced systems: Thermo-responsive hydrogel systems have been developed for pulsatile release. In these systems the polymer undergoes swelling or deswelling phase in response to the temperature which modulate drug release in swollen state developed indomethacin pulsatile release pattern in the temperature ranges between 200C and 300C by using reversible swelling properties of copolymers of N-isopropylacrylamide and butyrylacrylamide.

b. Chemical stimuli induced Pulsatile system Glucose-responsive release devices: In case of diabetes mellitus there is insulin rhythmic increase in the levels of glucose in the body requiring injection of the insulin at proper time. Several systems have been developed which are able to respond to changes in glucose concentration. One such system includes pH sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. When glucose concentration in the blood increases glucose oxidase converts glucose into gluconic acid which changes the pH of the system. This pH change induces swelling of the polymer which results in insulin release. Insulin by virtue of its action reduces blood glucose level and consequently gluconic acid level also gets decreased and system turns to the deswelling mode thereby decreasing the insulin release. Examples of the pH sensitive polymers includes N,dimethylaminoethyl methacrylate, chitosan, polyol etc.

c. **Inflammation-induced pulsatile release:** On receiving any physical or chemical stress, such as injury, fracture etc., and inflammation take place at the injured sites. During inflammation, hydroxyl radicals are produced from these inflammation- responsive cells .Yui and co-workers focused on the inflammatory induced hydroxyl radicals and designed drug delivery systems, which responded to the hydroxyl radicals and degraded in a limited manner. They used hyaluronic acid (HA) which is specifically degraded by the hyaluronidase or free radicals. Degradation of HA via the hyaluronidase is very low in a normal state of health. Degradation via hydroxyl radicals however, is usually dominant and rapid when HA is injected at inflammatory sites. Thus, it is possible to treat patients with inflammatory diseases like rheumatoid arthritis; using anti-inflammatory drug incorporated HA gels as new implantable drug delivery systems. [16,17]

d. **Drug release from intelligent gels responding to antibody concentration:** There are numerous kinds of bioactive compounds which exist in the body. Recently, novel gels were developed which responded to the change in concentration of bioactive compounds to alter their swelling/deswelling characteristics. Special attention was given to antigen-antibody complex formation as the cross-linking units in the gel, since such interaction are very specific. Utilizing the difference in association constants between polymerized antibodies and naturally derived antibodies towards specific antigens, reversible gel swelling/deswelling and drug permeation changes occurs.[18]

e. **pH sensitive drug delivery system:** Such type of pulsatile drug delivery system contains two components one is of immediate release type and other one is pulsed release which releases the drug in response to change in pH. In case of pH dependent system advantage has been taken of the fact that there exists different pH environment at different parts of the gastrointestinal tract. By selecting the pH dependent polymers drug release at specific location can be obtained. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, sodium carboxymethylcellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine. [19,20]

3. Externally regulated systems:

For releasing the drug in a pulsatile manner, another way can be the externally regulated systems in which drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation.

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Magnetically regulated system contains magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads developed different formulation for in vitro magnetically triggered delivery of insulin based on alginate spheres. In case of ultrasonically modulated systems, ultrasonic waves causes the erosion of the polymeric matrix thereby modulating drug release evaluated the effect of ultrasound (1 MHz) on the release rates of bovine insulin from ethylene vinyl alcohol copolymer matrices and reservoir-type drug delivery systems in which they found sharp drop in blood glucose levels after application of ultrasonic waves.[21,22]

VII. PRESENT SCENARIO AND FUTURE GOALS IN PDDS

In recent days PDDS attains higher position. The primary lead is, the drug releases when it is essential or needed only. The growth of development will be high. It has higher bioavailability. Patient compliance is good. Its main goal is to achieve higher popularity with a high range of benefits.

Nowadays pulsatile drug delivery systems are gaining importance in various disease conditions specifically in diabetes where dose is required at different time intervals. Among these systems, multi-particulate systems (e.g. pellets) offer various advantages over single unit which include no risk of dose dumping, flexibility of blending units with different release patterns, as well as short and reproducible gastric residence time. Multiparticulate systems consists pellets of different release profile which can be of any type like time dependent, pH dependent, micro flora activated system as discussed in the previous sections. Site and time specific oral drug delivery have recently been of great interest in pharmaceutical field to achieve improved therapeutic efficacy. Gastroretentive drug delivery system is an approach to prolong gastric residence time, thereby targeting sitespecific drug release in upper gastrointestinal (GI) tract. Floating drug delivery system (FDDS) and bioadhesive drug delivery are widely used techniques for gastro retention. Low density porous multiparticulate systems have been used by researchers for formulation of FDDS. Sharma and Pawar developed multiparticulate floating pulsatile drug delivery system using porous calcium silicate and sodium alginate for time and site specific drug release of meloxicam(Sharma & Pawar, 2006). Various pulsatile technologies have been developed on the basis of methodologies as discussed previously. These includes OROS® technology, CODAS® technology, CEFORM® technology, DIFFUCAPS® technology, Three-dimensional printing®, timerx® etc.

Table 2: Recently Available Various Chrono pharmaceutical Technologies

S.No	TECHNOLOGY	DESCRIPTION
1.	**DIFFUCAPS**[23]	It consists of a capsule with a single or more drug particles and it includes beads, pellets and granules. It is a orally disintegrating tablet or rapidly disintegrating tablet. It enhances the drug solubility. It reduces gastric mucosal irritation also food effect. Its mechanism involves multi particulate system.
2.	**Orbexa® technology**[24]	This technology involve granulation, spheronization and extrusion technique. The beads are used to controlled size and density which are perfect for formulation and controls the release of drug with the use of above techniques. It results in beads and they are coated with functional polymer membrane.

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3.	**IPDAS®**[25]	The intestinal protective drug absorption system is an oral system. NSAID"s like drugs are also used in this technique. This approach is applicable to gastro intestinal irritancy. It also involves multiparticulate system.
4.	**Geoclock®technology**[26]	It is a press coated tablet and oral drug delivery technology which allows the time release of active ingredient from the tablet. It is independent to PH and food. It can also use for multi pulse delivery. It is easily manufactured.
5.	**Controlled-onset- extended – release(COER-24) technology**[27]	It is used to control blood pressure and angina pectoris is Covera -HS tablet and the active ingredient is verapamil hydrochloride. It is one of the unique tablets which is made up of COER-24TM technology which is used to minimize cycle period fluctuations in heart rate and hyper tension.
6.	**Diffutab**[28]	It contains fusing mixtures [waxes and a hydrophilic polymer]. It is used to control drug release.
7.	**CODAS**[29]	Chronotherapeutic oral drug absorption system is a multiunit system for bed time dose. The main advantages include, it is independent offood and also PH for release of the drug.
8.	**Covera-HS**[30]	It is one of the approved preparations which is used to control high blood pressure and angina disease is Covera-HS. This Covera-HS is made up of COER-24TM technology which minimize regular cycle period fluctuations in heart rate and hypertension.
9.	**Minitabs**[31]	It is a small size(mm) tube shaped (2×2) which is covered with film layer to control the drug discharge rate. Minitabs are in gel nature

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10.	**OROS**[32]	This system delivers the drug reproducibly based on the time or site specific model in the GIT. The mechanism involve osmosis. Tablet is present in the form of reservoir and it is enclosed by the semipermeable membrane with a laser drilled orifice used to deliver the drug. The bilayer and tri layer tablet contain osmotic agent and drug, when it dissolves with Gastro intestinal fluid, the osmotic agent generate some pressure and it pushes the drug and it releases the drug through an orifice.

TABLE 3: SUMMARY OF VARIOUS RESEARCHES ON PULSATILE DRUG DELIVERY SYSTEM

S. NO.	NAME OF RESEARCHER /YEAR	TITLE OF THE WORK	OUTCOME OF WORK
1.	Kumar Prasanna P.S.S. et.al (2023)	Pulsatile drug delivery-a review	Pulsatile drug delivery system has carried off a lot of importance in drug delivery technology in the last 30 years and are gaining more importance in the field of pharmaceutical technologies.
2.	Lekha Sris. G et.al (2022)	Formulation and evaluation of time-controlled pulsatile release rosuvastatin press-coated tablets	The drug delivery system was designed to deliver the drug at a specific time for the patient suffering from Hyperlipidemia. The core tablets containing Rosuvastatin, anhydrous lactose, and different ratios of super disintegrants like croscarmellose sodium, and sodium starch glycolate, among six core tablets were formulated, and they were evaluated for post-compression parameters like Weight variation, Thickness, Hardness, Friability, Disintegration, and In-vitro drug release profile.
3.			

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	Dumpa Reddy Nagi et.al (2020)	Novel gastro retentive floating pulsatile drug delivery system produced via- hot melt extrusion and fused deposition modeling 3D printing	The study was performed to develop novel core-shell gastro-retentive floating pulsatile drug delivery systems using a hot-melt extrusion-paired fused deposition modeling (FDM) 3D printing and direct compression method
4.	Jaiswal Hema et.al (2019)	Pulsatile drug delivery system-an overview with special emphasis on losartan and captopril	This review article was designed to throw light on marketed techniques of pulsatile drug delivery and to investigate the pulsatile release of Losartan and Captopril, based on chrono therapeutic consideration. The principle rationale for the use of pulsatile release of the drugs is where a constant drug release is not required and drug delivery should be such that there is complete drug release after a lag time
5.	Swetha M et.al (2018)	Design and evaluation of compression coating pulsatile drug delivery system with natural and synthetic polymers	Aim of the present work is to formulate &evaluate an oral; time controlled pulsatile drug delivery system of Aceclofenac, based on chronotherapeutic approach for the treatment of Rheumatoid arthritis. An attempt made to develop chrono therapeutic drug delivery system of Aceclofenac with natural super disintegrates in core tablet and natural and synthetic polymers in different ratios as a coating. With pre-determined lag time of 6 hours by compression coating technique.
6.	Pandit Vinay et.al (2017)	Recent advancement and technological aspects of pulsatile drug delivery system- a laconic review	Pulsatile medication possess the potential to deliver the drugs in the therapy of diseases where drug dose is essential during sleep, drugs having greater first pass metabolism and absorption at precise location in digestive tract.

7.	Singh P Neha et.al (2016)	Pulsatile drug delivery system- a review	Current review article discussed the reasons for development of pulsatile drug delivery system, types of the disease in which pulsatile release is required, classification, advantages, and limitation, of pulsatile drug delivery system.
8.	Mali Digambar Audumbar et.al (2015)	An updated review on pulsatile drug delivery system	The current article focuses on the diseases requiring PDDS, methodologies involved for the existing systems, current situation and future scope, recent advances in PDDS and PDDS product currently available in the market.
9.	Rewar S et.al (2014)	Pulsatile drug delivery system- an overview	This article focuses on the pulsatile drug release, where the drug is released rapidly after a well defined lag-time, could be advantageous for many drugs or therapies. A pulse has to be designed in such a way thata complete and rapid drug release is achieved after the lag time so as to match body's circadian rhythms with the release of drug which increases the efficacy and safety of drugs by proportioning their peak plasma concentrations during the 24 hours in synchrony with biological rhythm.
10.	Singh Haribansh Narayan et.al (2013)	Pulsatile drug delivery system- drugs used in the pulsatile formulations	The article focuses on the review of literature concerning the disease requiring Pulsatile drug delivery system and the drugs used in the pulsatile formulations to target diseases.
11.	Shindhaye Supriya et.al	Technologies in pulsatile	The aim of this review is to

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	(2012)	drug delivery system	introduce the concept of chronopharmaceutics, to cover the technologies that have been developed to achieve pulsatile delivery such as Pulsincap®, Diffucaps®, CODAS®, and PULSYSTM; which follow various mechanism to render a sigmoidal drug release profile.
12.	Jain Deepika et.al (2011)	Recent technologies in pulsatile drug delivery system	This review covers methods and marketed technologies that have been developed to achieve pulsatile delivery.
13.	Patel D.Jigar et.al (2010)	Pulsatile drug delivery system- an user friendly dosage form	This article discusses about the various techniques are available for the pulsatile delivery like pH dependent systems, time dependent systems, etc. Pulsatile drug delivery system providing special and temporal delivery and increasing patient compliance.
14.	Tekade R. Avinash et.al (2009)	Development and evaluation of pulsatile drug delivery system using novel polymer	The aim of the present investigation was to develop a pulsatile drug delivery system based on an insoluble capsule body filled with theophylline microspheres and sealed with a swellable novel polymer plug isolated from the endosperm of seeds of higher plant Delonix regia family-Fabaceae.
15.	Hong-Liang Lin et.al (2008)	Release characteristics and in-vitro-in-vivo correlation of pulsatile pattern for a pulsatile drug delivery system activated by membrane rupture via osmotic pressure and swelling	This study attempted to characterize the influence of core and coating formulations on the release profiles to establish in vitro/in vivo correlations of pulsatile pattern for a pulsatile drug delivery system activated by membrane rupture based on

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			three core tablet formulations coated with various thicknesses of a semipermeable ethyl cellulose membrane plasticized with HPMC 606 at different ratios with/without adding various amounts of water to dissolve it in the coating solution.

VIII. CONCLUSION

Rapid advancement and newer developments in the field of drug delivery has led to the formulation of the pulsatile drug delivery system, which, on one hand, can be formulated with ease and, on the other hand, provide a significant amount of therapeutic benefits. These systems deliver the drug at right time, place and amount in the patient's body. The circadian disorders generally require chronopharmacotherapy, which can be easily accomplished by pulsatile drug delivery system in a very organized manner.

During the last two decades the pharmaceutical technology has grown leaps and bounds and with the advent of pulsatile drug delivery one can remain assured of accomplishment of goal for safe and effective therapy. There are a number of ailments that require that the drug/bioactive be delivered in a specific way. The same cannot be either achieved or the benefits are partial when it comes to the conventional dosage forms.

Significant modification and designing of the conventional delivery systems in the form of pulsatile delivery systems ensures the time-controlled pulsatile release of bioactive compounds, which is prerequisite in the treatment of such disorders. The etiology of the dreaded diseases can be linked to the release of the specific drugs through these systems, which would definitely result in the betterment of the therapy. Although several milestones have been reached in this respect, there are still some unexplored facets of pulsatile drug delivery that can open new vistas through better engineering of the same.

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